Application number	Applicant	Parties to exemption
3606-P	Valcor Engineering Corporation, Springfield, NJ.	3606
4453-P	E. I. du Pont de Nemours & Co., Inc. Wilmington, DE.	4453
5951-P	McKesson Chemical Company, Spartanburg, SC.	5951
6092-P	Hi-Pure Chemicals, Inc., Nazareth, PA.	6092
6602-P	Ethyl Corporation, Baton Rouge, LA.	6602
6702-P	Seragen, Inc., Boston, MA	6702
6926-P	Union Carbide Agricultural Products Company, Danbury, CT.	6926
7052-P	SAFT America Inc., Cockeysville, MD.	7052
7052-P	Electro-Flow Controls, Inc., Missouri City, TX.	7052
7052-P	Technical Oil Tool Corporation, Norman, OK.	7052
7052-P	In-Situ, Inc., Laramie, WY	7052
7835-P	Big Three Industries, Inc., Houston, TX.	7835
7890-P	Union Carbide Agricultural Products Company, Danbury, CT.	7890
7909-P	EMCO, Inc., Little Rock, AR	7909
8099-P	Union Carbide Corporation, Danbury, CT.	8099
8129-P	Disposal Control Service, Upland, CA.	8129
8129-P	Bunker Ramo Electronic Systems, Westlake Village, CA.	8129
8129-P	Containerized Chemical Disposal, Inc., Morovia, CA.	8129
8129-P	Solvent Service, Inc., San Jose, CA.	8129
8129-P	McDonnell Douglas Corporation, St. Louis, MO.	8129
8129-P	Varian Palto Alto, CA	8129
8445-P	McDonnell Douglas Corporation, St. Louis, MO.	8445
8554-P	Buckley Powder Company, Denver, CO.	8554
8877-P	Mallinckrodt, Inc., Paris, KY	8877
8877-P	KTI Chemicals, Incorporated, Danbury, CT.	8877

This notice of receipt of applications for renewal of exemptions and for party to an exemption is published in accordance with section 107 of the Hazardous Materials Transportation Act (49 U.S.C. 1806; 49 CFR 1.53(e)).

Issued in Washington, DC, on June 3, 1983.

J. R. Grothe,

Chief, Exemption Branch, Office of Hazardous Materials Regulation, Materials Transportation Bureau.

[FR Doc. 84-15491 Filed 6-8-83; 8:45 a.m.]

BILLING CODE 4910-60-M

Saint Lawrence Seaway Development Corporation

Advisory Board; Meeting

Pursuant to section 10(a)(2) of the Federal Advisory Committee Act (Pub. L. 92-463; 5 U.S.C. App. I) notice is hereby given of a meeting of the Advisory Board of the Saint Lawrence Seaway Development Corporation, to be held at 1:30 p.m., June 27, 1983, at the Corporation's Offices at 800 Independence Avenue, SW., Washington, D.C. The agenda for this meeting will be as follows: Opening Remarks; Consideration of Minutes of Past Meeting; Review of Programs; Business; Closing Remarks.

Attendance at meetings is open to the interested public but limited to the space available. With the approval of the Administrator, members of the public may present oral statements at the meeting. Persons wishing further information should contact, not later than June 23, 1983, Robert D. Kraft, Director, Plans and Policy Development, Saint Lawrence Seaway Development Corporation, 800 Independence Avenue, SW., Washington, D.C. 20591; 202/426-3574.

Any member of the public may present a written statement to the Advisory Board at any time.

Issued at Washington, D.C., on June 3, 1983.

Robert D. Kraft,

Director, Plans and Policy Development.

[FR Doc. 83-15382 Filed 6-8-83; 8:45 am]

BILLING CODE 4910-61-M

VETERANS ADMINISTRATION

Agency Form Under OMB Review

AGENCY: Veterans Administration.

ACTION: Notice

The Veterans Administration has submitted to OMB for review the following proposal for the collection of information under the provisions of the Paperwork Reduction Act (44 U.S.C. Chapter 35). This is a new data collection. The entry contains the following information: (1) The department or staff office issuing the form; (2) The title of the form; (3) The agency form number, if applicable; (4) How often the form must be filled out; (5) Who will be required or asked to report; (6) An estimate of the number of responses; (7) An estimate of the total number of hours needed to fill out the form; and (8) An indication of whether section 3504(H) of Pub. L. 96-511 applies.

ADDRESSES: Requests for further information, including copies of the proposed form and supporting documents may be obtained from Patricia Viers, Agency Clearance Officer (004A2), Veterans Administration, 810 Vermont Avenue, NW, Washington, DC 20420 (202) 389-2146. Comments and questions about the items on this list should be directed to the Office of Information and Regulatory Affairs of OMB, Attention: Rich Shepard, Desk Officer for Veterans Administration, 726 Jackson Place, NW, Washington, DC 20503, (202) 395-6880.

DATES: Comments on the form should be directed to the OMB Desk Officer within 60 days of this notice.

Dated: May 23, 1983.

Dominick Onorato,

Associate Deputy Administrator for Information Resources Management.

Category: New

Department: Department of Medicine and Surgery

Title of form: Former Prisoner of War Medical History

Agency form #: 10-0048

How often the form must be filled out: One time, nonrecurring

Estimate of the number of responses: 10,000

Estimate of the total number of hours needed: 5,000 hrs.

Section 3504(H) of Pub. L. 96-511: Not applicable

[FR Doc. 83-15432 Filed 6-8-83; 8:45 am]

BILLING CODE 8320-01-M

Performance Review Board Members

AGENCY: Veterans Administration.

ACTION: Notice.

SUMMARY: Under the provisions of 5 U.S.C. 4314(c)(4) agencies are required to publish a notice in the **Federal Register** of the appointment of Performance Review Board (PRB) members. This list amends the list of members of the Veterans Administration Performance Review Board which was published in the **Federal Register** 47 FR 42862 and 42863, dated September 29, 1982.

EFFECTIVE DATE: May 6, 1983.

FOR FURTHER INFORMATION CONTACT: K. Joyce Edwards, Office of Personnel and Labor Relations (05A3), Veterans Administration, 810 Vermont Avenue, NW., Washington, D.C. 20420 (202-389-3423).

The members of the VA Performance Review Board are:

Chairperson.— Everett Alvarez, Jr., Deputy Administrator.

Members.—Anthony J. Principi, Associate Deputy Administrator for Congressional and Public Affairs, Dominick Onorato, Associate Deputy Administrator for Information Resources Management, William F. Sullivan, Associate Deputy Administrator for Logistics, Donald L. Custis, M.D., Chief Medical Director, Dorothy L. Starbuck, Chief Benefits Director, Paul T. Bannai, Chief Memorial Affairs Director, John P. Murphy, General Counsel, Kenneth E. Eaton, Chairman, Board of Veterans Appeals, Jack J. Sharkey, Director, Office of Data Management and Telecommunications, Conrad Hoffman, Director, Office of Budget and Finance, Joseph Mancias, Jr., Director, Office of Public and Consumer Affairs, Raymond S. Blunt, Director, Office of Program Planning and Evaluation, William A. Salmond, Director, Office of Construction, Michael Rudd, Director, Office of Personnel and Labor Relations, Clyde C. Cook, Director, Office of Procurement and Supply, Robert W. Schultz, Director, Office of Reports, and Statistics, Renald P. Morani, Assistant Inspector General for Policy, Planning and Resources.

Dated: June 2, 1983.

Everett Alvarez, Jr.,

Deputy Administrator.

[FR Doc. 83-15433 Filed 6-8-83; 8:45 am]

BILLING CODE 8320-01-M

Sunshine Act Meetings

Federal Register
Vol. 48, No. 112
Thursday, June 9, 1983

This section of the FEDERAL REGISTER contains notices of meetings published under the "Government in the Sunshine Act" (Pub. L. 94–409) 5 U.S.C. 552b(e)(3).

CONTENTS

1

COMMODITY FUTURES TRADING COMMISSION

TIME AND DATE: 11 a.m., Friday, June 17, 1983.

PLACE: 2033 K Street NW., Washington, D.C., Eighth floor conference room.

STATUS: Closed.

MATTERS TO BE CONSIDERED:

Surveillance Briefing

CONTACT PERSON FOR MORE INFORMATION: Jane Stuckey, 254–6314.

[S-818-83 Filed 6-7-83; 2:03 pm]

BILLING CODE 6351-01-M

2

COMMODITY FUTURES TRADING COMMISSION

TIME AND DATE: 2 p.m., Thursday, June 16, 1983.

PLACE: 2033 K Street NW., Washington, D.C., Eighth floor conference room.

STATUS: Closed.

MATTERS TO BE CONSIDERED:

Judicial Session

CONTACT PERSON FOR MORE INFORMATION: Jane Stuckey, 254–6314.

[S-819-83 Filed 6-7-83; 2:03 P.m.]

BILLING CODE 6351-01-M

3

COMMODITY FUTURES TRADING COMMISSION

TIME AND DATE: 11 a.m., Friday, June 10, 1983.

PLACE: 2033 K Street NW., Washington, D.C., eighth floor conference room.

STATUS: Closed.

MATTERS TO BE CONSIDERED:

Surveillance Briefing

CONTACT PERSON FOR MORE INFORMATION: Jane Stuckey, 254–6314.

[S-820-83 Filed 6-7-83; 2:03 pm]

BILLING CODE 6351-01-M

4

COMMODITY FUTURES TRADING COMMISSION

"FEDERAL REGISTER" CITATION OF PREVIOUS ANNOUNCEMENT:

PREVIOUSLY ANNOUNCED TIME AND DATE OF THE MEETING: 11 a.m., Friday, June 10, 1983.

CHANGES IN THE MEETING: Rescheduled to: 11 a.m., Thursday, June 9, 1983.

[S-821-83 Filed 6-7-83; 2:03 pm]

BILLING CODE 6351-01-M

5

COMMODITY FUTURES TRADING COMMISSION

TIME AND DATE: 10 a.m., Thursday, June 9, 1983.

PLACE: 2033 K Street NW., Washington, D.C., fifth floor hearing room.

STATUS: Open.

MATTERS TO BE CONSIDERED:

Contract Market Application Fees

CONTACT PERSON FOR MORE INFORMATION: Jane Stuckey, 254–6314.

[S-822-83 Filed 6-7-83; 2:03 pm]

BILLING CODE 6351-01-M

6

COMMODITY FUTURES TRADING COMMISSION

TIME AND DATE: 10:30 a.m., Thrusday, June 9, 1983.

PLACE: 2033 K Street NW., Washington, D.C., 5th floor hearing room.

STATUS: Closed.

MATTERS TO BE CONSIDERED:

Discussion of mandated studies.

CONTACT PERSON FOR MORE INFORMATION: Jane Stuckey, 254–6314.

[S-823-83 Filed 6-7-83; 2:03 pm]

BILLING CODE 6351-01-M

7

FEDERAL DEPOSIT INSURANCE CORPORATION

Agency Meeting

Pursuant to the provisions of the "Government in the Sunshine Act" (5 U.S.C. 552b), notice is hereby given that at 2:30 p.m. on Monday, June 13, 1983, the Federal Deposit Insurance Corporation's Board of Directors will meet in closed session, by vote of the Board of Directors, pursuant to sections 552b (c)(2), (c)(4), (c)(6), (c)(8), (c)(9)(A)(ii), (c)(9)(B), and (c)(10) of Title 5, United States Code, to consider the following matters:

Summary Agenda: No substantive discussion of the following items is anticipated. These matters will be resolved with a single vote unless a member of the Board of Directors requests that an item be moved to the discussion agenda.

Recommendations with respect to the initiation, termination, or conduct of administrative enforcement proceedings (cease-and-desist proceedings, termination-of-insurance proceedings, suspension or removal proceedings, or assessment of civil money penalties) against certain insured banks or officers, directors, employees, agents or other persons participating in the conduct of the affairs thereof:

Names of persons and names and locations of banks authorized to be exempt from disclosure pursuant to the provisions of subsections (c)(6), (c)(8), and (c)(9)(A)(ii) of the "Government in the Sunshine Act" (5 U.S.C. 552b (c)(6), (c)(8), and (c)(9)(A)(ii)).

Note.—Some matters falling within this category may be placed on the discussion agenda without further public notice if it becomes likely that substantive discussion of those matters will occur at the meeting.

Discussion Agenda:

Application for Federal deposit insurance:

Lewis County Bank, a proposed new bank to be located at the southeast corner of West Linden Street and North Court Street, Hohenwald, Tennessee.

Application for consent to transfer assets in consideration of the assumption of deposit liabilities:

Monroe Savings Bank, Rochester, New York, a federally-chartered savings bank insured by the Federal Deposit Insurance Corporation, for consent to transfer certain assets to Empire of America, FSA, Southfield, Michigan, a federal savings association not insured by the Federal Deposit Insurance Corporation, in consideration of the assumption of liabilities for deposits made in the Corning,

Dansville and Hornellsville, New York, branches of Monroe Savings Bank.

Application pursuant to section 19 of the Federal Deposit Insurance Act for consent to service of a person convicted of an offense involving dishonesty or a breach of a trust as a director, officer, or employee of an insured bank:

Name of person and of bank authorized to be exempt from disclosure pursuant to provisions of subsections (c)(6), (c)(8), and (c)(9)(A)(ii) of the "Government in the Sunshine Act" (5 U.S.C. 552b (c)(6), (c)(8), and (c)(9)(A)(ii)).

Request for relief from adjustment for violations of Regulation Z:

Name and location of bank authorized to be exempt from disclosure pursuant to the provisions of subsections (c)(8) and (c)(9)(A)(ii) of the "Government in the Sunshine Act" (5 U.S.C 552b (c)(8) and (c)(9)(A)(ii)).

Recommendation regarding the liquidation of a bank's assets acquired by the corporation in its capacity as receiver, liquidator, or liquidating agent of those assets:

Memorandum and Resolution re: The Metro Bank of Huntington, Inc. Huntington, West Virginia

Personnel actions regarding appointments, promotions, administrative pay increases, reassignments, retirements, separations, removals, etc.:

Names of employees authorized to be exempt from disclosure pursuant to provisions of subsections (c)(2) and (c)(6) of the "Government in the Sunshine Act" (5 U.S.C. 552b (c)(2) and (c)(6)).

The meeting will be held in the Board Room on the sixth floor of the FDIC Building located at 550 17th Street, N.W., Washington, D.C.

Requests for further information concerning the meeting may be directed to Mr. Hoyle L. Robinson, Executive Secretary of the Corporation, at (202) 389–4425.

Dated: June 6, 1983.

Federal Deposit Insurance Corporation.

Hoyle L. Robinson,

Executive Secretary.

[S-816-83 Filed 6-7-83; 11:51 am]

BILLING CODE 6714-01-M

8

FEDERAL DEPOSIT INSURANCE CORPORATION

Agency Meeting

Pursuant to the provisions of the "Government in the Sunshine Act" (5 U.S.C. 552b), notice is hereby given that the Federal Deposit Insurance Corporation's Board of Directors will meet in open session at 2 p.m. on Monday, June 12, 1983, to consider the following matters:

Summary Agenda: No substantive discussion of the following items is anticipated. These matters will be resolved with a single vote unless a member of the Board of Directors requests that an item be moved to the discussion agenda.

Disposition of minutes of previous meetings.

Application for consent to merge and establish three branches:

Community First Bank, Bakersfield, California, an insured State nonmember bank, for consent to merge, under its charter and title, with Growers and Merchants State Bank, Selma, California, and to establish the three offices of Growers and Merchants State Bank as branches of the resultant bank.

Applications for consent to purchase assets and assume liabilities and establish one branch:

Le Mars Savings Bank, Le Mars, Iowa, an insured State nonmember bank, for consent to purchase the assets of and assume the liability to pay deposits made in Farmers Savings Bank, Struble, Iowa, and to establish the sole office of Farmers Savings Bank as a branch of Le Mars Savings Bank.

Hamilton Bank, Lancaster, Pennsylvania, an insured State nonmember bank, for consent to purchase certain assets of and assume the liability to pay deposits made in the Lebanon Plaza Branch of the Commonwealth National Bank, Harrisburg, Pennsylvania, and to establish that office as a branch of Hamilton Bank.

Recommendations regarding the liquidation of a bank's assets acquired by the Corporation in its capacity as receiver, liquidator, or liquidating agent of those assets:

Case No. 45,691—The Greenwich Savings Bank, New York, New York

Case No. 45,692-SR—The Bank of Woodson, Woodson, Texas

Memorandum and Resolution re: The Farmers State Bank, Protection, Kansas

Reports of committees and officers:

Minutes of actions approved by the standing committees of the Corporation pursuant to authority delegated by the Board of Directors.

Reports of the Division of Bank Supervision with respect to applications, requests, or actions involving administrative enforcement proceedings approved by the Director or Associate Director (Administration and Corporate Applications) of the Division of Bank Supervision and the various Regional Directors pursuant to authority delegated by the Board of Directors.

Report of the Director, Office of Corporate Audits and Internal Investigations:

Audit Report re: Reimbursable Expenses Billed to the FDIC by the Firm of Roth, Kudler, Berner and Company, dated May 12, 1983.

Discussion Agenda:

No matters scheduled.

The meeting will be held in the Board Room on the sixth floor of the FDIC Building located at 550 17th Street, N.W., Washington, D.C.

Requests for further information concerning the meeting may be directed to Mr. Hoyle L. Robinson, Executive Secretary of the Corporation, at (202) 389–4425.

Dated: June 6, 1983.

Federal Deposit Insurance Corporation.

Hoyle L. Robinson,

Executive Secretary.

S-817-83 Filed 6-7-83; 11:51 am]

BILLING CODE 6714-01-M

9

FEDERAL DEPOSIT INSURANCE CORPORATION

Changes in Subject Matter of Agency Meeting

Pursuant to the provisions of subsection (e)(2) of the "Government in the Sunshine Act" (5 U.S.C. 552b(e)(2), notice is hereby given that at its open meeting held at 2 p.m. on Monday, June 6, 1983, the Corporation's Board of Directors determined, on motion of Chairman William M. Isaac, seconded by Director Irvin H. Sprague (Appointive), concurred in by Mr. H. Joe Selby, acting in the place and stead of Director C. T. Conover (Comptroller of the Currency), that Corporation business required the withdrawal from the agenda for consideration at the meeting, on less than seven days' notice to the public, of the following matter:

Request of Dakota Bank of Wahpeton, a proposed new bank to be located at 1005 Dakota Avenue, Wahpeton, North Dakota, for reconsideration of a previous denial of an application for Federal deposit insurance.

The Board further determined, by the same majority vote, that Corporation business required the addition to the agenda for consideration at the meeting, on less than seven days' notice to the public, of the following matters:

Application of Hoosier State Bank of Indiana, Hammond, Indiana, for consent to establish a branch within the Strack & Vantil Grocery Store, Routes 30 and 41, Schererville, Indiana.

Request of the Philadelphia Savings Fund Society, Horsham Township (P.O. Horsham), Pennsylvania, for a waiver of the time deposit early withdrawal penalty.

By the same majority vote, the Board further determined that no earlier notice

of these changes in the subject matter of the meeting was practicable.

Dated: June 6, 1983.

Federal Deposit Insurance Corporation.

Hoyle L. Robinson

Executive Secretary.

[S-827-83 Filed 6-7-83; 3:07 pm]

BILLING CODE 6714-01-M

10

FEDERAL DEPOSIT INSURANCE CORPORATION

Changes in Subject Matter of Agency Meeting

Pursuant to the provisions of subsection (e)(2) of the "Government in the Sunshine Act" (5 U.S.C. 552b(e)(2)), notice is hereby given that at its closed meeting held at 2:30 p.m. on Monday, June 6, 1983, the Corporation's Board of Directors determined, on motion of Chairman William M. Isaac, seconded by Director Irvine H. Sprague (Appointive), concurred in by Mr. H. Joe Selby, acting in the place and stead of Director C. T. Conover (Comptroller of the Currency), that Corporation business required the addition to the agenda for consideration at the meeting, on less than seven days' notice to the public, of the following matters:

Request of Indian Springs State Bank, Kansas City, Kansas, for an extension of time within which to relocate the main office from 4601 State Avenue to 4810 State Avenue, Kansas City, Kansas.

Application pursuant to section 19 of the Federal Deposit Insurance Act for consent to service of a person convicted of an offense involving dishonesty or a breach of a trust as a director, officer, or employee of an insured bank: Name of person and of bank authorized to be exempt from disclosure pursuant to the provisions of subsections (c)(6), (c)(8), and (c)(9)(A)(ii) of the "Government in the Sunshine Act" (5 U.S.C. 552b (c)(6), (c)(8), and (c)(9)(A)(ii)).

Recommendation regarding the liquidation of a bank's assets acquired by the Corporation in its capacity as receiver, liquidator, or liquidating agent of those assets:

Case No. 45,694-L (Addendum)—The Ina State Bank, Ina, Illinois

The Board further determined, by the same majority vote, that no earlier notice of these changes in the subject matter of the meeting was practicable; that the public interest did not require consideration of the matters in a meeting open to public observation; and that the matters could be considered in a closed meeting by authority of subsection (c)(4), (c)(6), (c)(8), (c)(9)(A)(ii), and (c)(9)(B) of the "Government in the Sunshine Act" (5 U.S.C. 552b (c)(4), (c)(6), (c)(8), (c)(9)(A)(ii), and (c)(9)(B)).

Dated: June 6, 1983.

Federal Deposit Insurance Corporation

Hoyle L. Robinson,

Executive Secretary.

[S-828-83 Filed 6-7-83; 3:07 pm]

BILLING CODE 6714-01-M

11

FEDERAL ELECTION COMMISSION

DATE AND TIME: Tuesday, June 14, 1983, 10 a.m.

PLACE: 1325 K Street, NW., Washington, D.C.

STATUS: This meeting will be closed to the public.

MATTERS TO BE CONSIDERED: Compliance, Personnel, Litigation, Audits.

PERSON TO CONTACT FOR MORE INFORMATION: Mr. Fred Eiland, Information Officer, telephone: 202-523-4065.

Marjorie W. Emmons,

Secretary of the Commission.

[S-829-83 Filed 6-7-83; 3:38 pm]

BILLING CODE 6715-01-M

12

FEDERAL MARITIME COMMISSION

TIME AND DATE: 9 a.m., June 15, 1983.

PLACE: Hearing Room One, 1100 L Street NW., Washington, D.C. 20573

STATUS: Parts of the meeting will be open to the public. The rest of the meeting will be closed to the public.

MATTERS TO BE CONSIDERED: Portions open to the public:

1. Agreement No. 8900-20: Modification of the "8900" Lines Rate Agreement to permit the establishment of open rates.

2. Special Docket No. 1021—Application of Korea Shipping Corporation for the Benefit of Sunkyong Magnetic Ltd; Special Docket No. 1022—Application of Hanjin Container Lines, Ltd. for the Benefit of Latex Gloves Co., Inc.; Special Docket No. 1023—Application of American President Lines, Ltd. for the Benefit of Lux Chemical Corp.; Special Docket No. 1024—Application of Yamashita-Shinnihon Steamship Co., Ltd. for the Benefit of Melco Sales Singapore Pte., Ltd.—Consideration of Order of Discontinuance.

Portion closed to the public:

1. Volume Incentive Program of Agreements Nos. 10107 and 10108.

CONTACT PERSON FOR MORE INFORMATION: Francis C. Hurney, Secretary (202) 523-5725.

[S-826-83 Filed 6-7-83; 2:18 pm]

BILLING CODE 6730-01-M

13

NATIONAL CREDIT UNION ADMINISTRATION

Changes in Date and Subject of Board Meeting

The previously announced closed meeting of the National Credit Union Administration scheduled for 4 p.m., Wednesday, May 11, 1983 was changed to Thursday, May 12, 1983.

The National Credit Union Administration Board also determined that its business required that the previously announced closed meeting on Wednesday, May 11, 1983 changed to Thursday, May 12, 1983 include the following additional item, which was closed to public observation.

Budget Allocation. Closed purusant to exemption (2).

The Board voted unanimously to add this item to the closed agenda.

Earlier announcement of these changes was not possible.

The previously announced items were:

1. Approval of Minutes of Previous Closed Meetings.

2. Requests from Federally insured credit unions for special assistance to prevent liquidation under Section 208(a)(1) of the Federal Credit Union Act. Closed pursuant to exemptions (8) and (9)(A)(ii).

3. Requests for special assistance under Section 208(a)(2) of the Federal Credit Union Act. Closed pursuant to exemptions (8) and (9)(A)(ii).

4. Requests for emergency mergers under Section 205(h) of the Federal Credit Union Act with special assistance under Section 208(a)(2) of the Federal Credit Union Act. Closed pursuant to exemptions (8) and (9)(A)(ii).

5. Proposed Memorandum of Agreement between NCUA and a Federal Credit Union. Closed pursuant to exemptions (8) and (9)(A)(ii).

6. Personnel Actions. Closed pursuant to exemptions (2) and (6).

The meeting was held at 2:54 p.m., Sheraton Centre Hotel, 811 7th Avenue (7th and 53rd Street), New York, New York 10019.

CONTACT PERSON FOR MORE INFORMATION: Rosemary Brady, Secretary of the Board, telephone (202) 357-1100.

[S-824-83 Filed 6-7-83; 2:14 pm]

BILLING CODE 7535-01-M

14

NATIONAL CREDIT UNION ADMINISTRATION

TIME AND DATE: 9 a.m., Tuesday, June 14, 1983.

PLACE: Seventh floor board room, 1776 G Street NW., Washington, D.C. 20456.

STATUS: Open.

MATTERS TO BE CONSIDERED:

1. Approval of Minutes of Previous Open Meeting.
2. Review of Central Liquidity Facility Lending Rate.

* * * * *

TIME AND DATE: 2 p.m., Monday, June 13, 1983.

PLACE: Seventh floor board room, 1776 G Street NW., Washington, D.C. 20456.

STATUS: Closed.

MATTERS TO BE CONSIDERED:

1. Approval of Minutes of Previous Closed Meeting.
2. Administrative Action under Section 206 of the Federal Credit Union Act. Closed pursuant to exemptions (8) and (9)(A)(ii).
3. Requests from Federally insured credit unions for special assistance to prevent liquidation under Section 208(a)(1) of the Federal Credit Union Act. Closed pursuant to exemptions (8) and (9)(A)(ii).
4. Personnel Actions. Closed pursuant to exemptions (2) and (6).

CONTACT PERSON FOR MORE INFORMATION: Rosemary Brady, Secretary of the Board, Telephone (202) 357–1100.

[S-825-83 Filed 6-7-83; 2:14 pm]

BILLING CODE 7535-01-M

federal register

Thursday
June 9, 1983

Part II

Environmental Protection Agency

Fuel Economy of Motor Vehicles; Revisions To Improve Fuel Economy Labeling and the Fuel Economy Data Base

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 600

[AMS-FRL 2302-7, Docket No. A-80-32]

Fuel Economy of Motor Vehicles; Revisions To Improve Fuel Economy Labeling and the Fuel Economy Data Base

AGENCY: Environmental Protection Agency.

ACTION: Notice of proposed rulemaking.

SUMMARY: This notice proposes to amend the motor vehicle fuel economy regulations for fuel economy labeling and for submitting fuel economy data for calculating Corporate Average Fuel Economy (CAFE) and label values. EPA proposes that these amendments take effect beginning with the 1985 model year.

Accurate and reliable fuel economy information is essential to allow the free market to exert its influence on what vehicles are produced. The primary purpose of this proposal is to increase the credibility and usefulness of EPA's fuel economy information to prospective new-car buyers. We believe this proposal will accomplish this goal without significant regulatory increases.

The major proposals in this rulemaking would: (1) Mathematically adjust laboratory fuel economy label values to correct for the average differences between the fuel economy measured in the laboratory and actual in-use experience, (2) require fuel economy labels to be revised during the model year if label values decrease by 1.0 mpg due to certain design changes and following a mid-year general recalculation, (3) require that the minimum data used in label calculations be more representative of projected sales, (4) require that both city and highway adjusted fuel economy values appear on each fuel economy label, and (5) establish a standard label format to more clearly highlight the fuel economy values and improve the consumer's ability to compare products.

DATE: Public Comment: Comments on the proposed rule must be received by September 1, 1983. The dates of the hearing will be Tuesday, and Wednesday, July 26 and 27, 1983.

ADDRESS: Comments in response to this NPRM should be submitted to the U.S. Environmental Protection Agency, Central Docket Section (A-130), Gallery 1, West Tower Lobby, Waterside Mall, 401 M Street, SW., Washington, D.C. 20460, Attn: Docket No. A-80-32.

A hearing will be held at the Ann Arbor Huron High School in Ann Arbor, Michigan, 2727 Fuller Road. On the first day the hearing will be convened at 9:00 a.m. and will adjourn at 5:00 p.m. If a second day is necessary to complete the business of the hearing, the hearing will reconvene at 9:00 a.m.

FOR FURTHER INFORMATION CONTACT: Clifford D. Tyree, Certification Division, Office of Mobile Sources, Environmental Protection Agency, 2565 Plymouth road, Ann Arbor, MI 48105; (313) 668-4310.

SUPPLEMENTARY INFORMATION:

Participation in the Public Hearing

Any person desiring to make a statement at the hearing or to submit material for the hearing record should contact Judy Faye Carmickle (313-668-4440) to schedule a time at the hearing. These scheduled to testify or those planning to submit material at the hearing should provide written confirmation of their interest, together with at least one copy of the proposed statement or material, for inclusion in the record. All such documents should be submitted to EPA at the address below no later than Tuesday, July 19, 1983. It is strongly requested, but not required, that at least 100 copies accompany any documents which cannot be submitted prior to the start of the hearing.

Participants are advised to adhere to these guidelines if possible. Documents submitted late may not receive full staff consideration prior to the hearing. Further, participants who submit documents on the scheduled day of the appearance, without the requested 100 copies, may be rescheduled for a later time or session of the hearing if duplication of the documents cannot be completed by EPA prior to the scheduled time of appearance.

The record of the hearing will be left open for 30 days following the close of the hearing to allow submission of rebuttal and supplementary information.

Mr. Richard D. Wilson is hereby designated as the Presiding Officer of the hearing. He will be responsible for maintaining order, excluding irrelevant or repetitious material, scheduling presentations, and, to the extent possible, notifying participants of the time at which they may appear. The hearing will be conducted informally. Technical rules of evidence will not apply.

The present national fuel economy testing program performs three functions: (1) It generates general fuel economy values for each model type and makes these values available to the public on individual vehicle fuel economy labels and in the *Gas Mileage Guide (Guide)* pursuant to 15 U.S.C. 2006, (2) it determines manufacturers' compliance with the CAFE requirements established in accordance with 15 U.S.C. 2002, (3) it establishes, in accordance with the National Energy Conservation and Policy Act (NECPA), manufacturers' "Gas Guzzler Tax" liability based on the general fuel economy label calculations.

In recent years, EPA, other government agencies, the U.S. Congress, and consumers have been concerned about apparent differences between the EPA fuel economy estimates and the actual fuel economy performance of vehicles in use. In general, these differences arise from travel environment, owner travel and driving habits, and vehicle maintenance. An EPA report to Congress, entitled "Passenger Car Fuel Economy: EPA and Road," EPA-460/3-80-010, published September 1980, shows that since 1976, fuel economy label and *Guide* figures have been higher, on the average (termed "shortfall"), than actual in-use fuel economy. This discrepancy has caused considerable consumer dissatisfaction and lack of confidence in EPA's fuel economy estimates.

Congress addressed this problem in public hearings of the House Subcommittee on Environment, Energy, and Natural Resources on January 29 through February 1, 1980.[1] The subcommittee concluded that the fuel economy information provided to consumers did not adequately reflect in-use fuel economy and that EPA possesses the authority to make changes in the fuel economy program that will improve the accuracy of the fuel economy data. The subcommittee consequently recommended that EPA devise a new system for labeling new vehicles with fuel economy values that most drivers can reasonably expect to experience. The subcommittee also recommended that EPA tighten its test procedures for determining compliance with Federal CAFE standards in order to eliminate actual or potential loopholes that introduce inaccuracies in EPA's approximation of in-use fleet average fuel economy. EPA has also been assessing its fuel economy testing program to improve the usefulness and accuracy of the fuel economy information it provides to the public and to improve the data base from which fuel economy values are derived.

On September 29, 1980, EPA published an advance notice of proposed

[1] Seventeenth Report by the Committee on Government Operations, Union Calendar No. 582, House Report No. 96-948, May 13, 1980.

rulemaking (ANPRM) for this proposed rule. The ANPRM presented several courses of action that EPA was considering for improvements in the fuel economy program and requested comments on those ideas. EPA received comments from a number of sources that included concerned citizens and consumer groups as well as major automobile manufacturers. This NPRM proposes changes that have resulted from EPA's desire to provide consumers with fair and accurate fuel economy information. Copies of specific comments on the ANPRM are available for public inspection in the EPA public docket presented in the **ADDRESS** section of this notice.

I. History and Background

In order to minimize the length of this notice EPA has not attempted to provide a detailed description of how the current program works or how it evolved. To the extent possible, we have presented the proposals in a manner that will not require extensive fuel economy program knowledge in order to understand them. The public docket for this rulemaking (Public Docket No. A–80–32) contains a report entitled *History and Description of the EPA Motor Vehicle Fuel Economy Program* which briefly describes the history and procedures of the current fuel economy program.

II. Description of the Proposed Modifications

A. In-Use Adjustments for Label Values

Many studies and analyses have been conducted to characterize the differences between EPA fuel economy estimates and in-use performance.[2] Two typical conclusions are that: (1) In-use fuel economy is significantly lower than EPA estimates and (2) because of these differences, consumer confidence in the label values has suffered. While a small portion of the differences could be eliminated by improved data representation and label updating (discussed later in this proposal), there would remain an offset between the advertised fuel economy values and the fuel economy achieved in use because of the different operating conditions between laboratory testing and in use. These laboratory conditions do not reflect changes in climate, road conditions, driving patterns, and other factors that affect in-use fuel economy.

In order to account for differences between EPA laboratory results and actual in-use experience, EPA proposes to calculate fuel economy values according to current procedures and then "discount" these values by an adjustment factor. EPA proposes that the adjustments be made by multiplying the city model type fuel economy value by 0.90 and the highway model type fuel economy by 0.78. The data and the procedures used to arrive at these factors are contained in an internal EPA report dated November 3, 1982, "Adjustments to EPA Fuel Values—Stage II Results." (This document is contained in the docket for this rulemaking.) EPA requests comments on the data and methodology used to derive these factors and may modify the factor as appropriate, based on comments received.

EPA proposes that only the adjusted fuel economy values appear on labels. However, EPA requests comments on alternative methods of presenting this information, pointing out specific advantages. For example, one alternative was suggested by the Office of Management and Budget (OMB) following its review of this proposal.[3] OMB suggested that rather than depicting single fuel conomy values on the label, the fuel economy estimates would be presented in a narrative form that includes a disclaimer for the unadjusted values. Both the unadjusted values and an adjustment factor would be presented. However, EPA believes that a "fine print" disclaimer is not useful since consumers most likely would not read it. Therefore, under this alternative, all lettering in the above fuel economy statement would be of the same size and prominence, including the fuel economy values. For example, under this alternative, the label fuel economy estimate for a given value (city or highway) could read as follows:

The [City, Highway] fuel economy estimate is —— m.p.g.; however, actual [City, Highway] fuel economy will likely average —— percent lower.

EPA is not proposing a set timetable for updating the adjustment factors. However, the Agency will continue to collect in-use data to review the status of the validity of the factors. If it appears appropriate to change the adjustment factors, EPA will publish proposed amendments and provide an appropriate leadtime before they are adopted. EPA requests comments on how to best collect such information and what minimum leadtime is necessary before revised factors can be used.

EPA also requests comments on ways to minimize consumer confusion in the first year of transition to adjusted fuel economy estimates. This confusion could result from consumers not being informed of (or not understanding) the reason for the fuel economy value decreases as compared to similar or identical vehicles of the previous model year. Manufacturers may also have problems highlighting fuel economy improvements for particular models when the adjustments bring the estimates below the previous year's estimates. EPA is open to suggestions as to how to best inform the public and to highlight fuel economy improvements.

B. Minimum Data Requirements for Labeling

The current minimum data requirement to establish a label value is one test per base level.[4] If the manufacturer has met the minimum data requirements by testing an emission test car, no additional testing is required for that base level to establish a label value. (If *no* previous data had been generated for a base level, the manufacturer must submit data from the highest projected sales configuration in the base level.) This can result in a base level represented by very low sales configurations. Because the base level fuel economy is sales-weighted into the model type label value using the *entire* base level sales, this single low sales configuration would have a disproportionate influence on the label value.

EPA has estimated the effect of this problem by projecting the likely fuel economy of untested subconfigurations and recalculating the label values for comparison. The results of this analysis show three percent of all 1980 vehicles were labeled 2 mpg or more too high, implying that the current system causes a portion of vehicles sold to be misrepresented simply because of data requirements and calculation methods. Although the number of labels affected is small, we are concerned that these

[2] The docket to this proposed rulemaking, A–80–32, contains numerous supporting documents and technical analyses. Note that because of revisions to this notice while in draft, EPA documents which are dated prior to July 1982 which describe the "proposed" rulemaking do not necessarily reflect the final proposals of this NPRM.

[3] Executive Order 12291 requires that all proposed regulations be reviewed by the Office of Management and Budget before being published. OMB commented in a letter to the Administrator dated June 2, 1983 (available in the public docket). OMB expressed a concern that label values with only the adjusted fuel economy values would imply more accuracy in the value than warranted. Specifically, the concern is that the public will perceive the adjusted values as predictions of the fuel economy each individual consumer will receive rather than representing an estimate of average performance to aid in comparison shopping as is intended.

[4] A base level is defined as a unique combination of vehicles with the same basic engine, inertia weight class, and transmission class. A complete listing of definitions can be found in 40 CFR 600.002–81.

biased label values can be extensively used, perhaps even emphasized in manufacturers' advertising. Further, without some change in the regulations, the situation could become worse in a future model year as manufacturers try to achieve continual increases in their label values.

EPA considered several alternative solutions to this problem. The first alternative was to test all configurations to establish label values. This was rejected as too burdensome and costly. The second alternative was to require minimum sales representation for test data in the label calculation. This was rejected since it could still greatly increase the manufacturers' testing burdens prior to model introduction and would increase label testing for models that are adequately covered under the current system. The third option was to retain the current testing requirements, but use analytical procedures to estimate test values for all subconfigurations. The analytical values and the actual test values would be used in sales-weighted label calculations, thus reflecting all designs at their proper sales weight. (This alternative is discussed further in Section III.E of this preamble.) EPA rejected this alternative since it would be a complex and controversial solution impacting all label calculations rather than centering only on the expected small number of problem labels.

Since our analysis suggests that this problem may be limited to a small number of model types that are not covered adequately by the current requirements, EPA proposes a simple solution whereby each base level must be represented at least by data from the highest projected sales configuration within the base level. This should affect only a small fraction of base levels. (In the 1982 model year, approximately 7 percent of the base levels were not represented by the high sales configuration for labeling.)

We do not expect that this requirement would cure all problem cases. However, it will correct some of the overstated label values and, more importantly, place limitations on a manufacturer's ability to overstate label values further by testing only vehicles with very low sales. Thus, this requirement would target only potential problem areas at a very small burden for manufacturers. The actual number of tests performed annually should not increase since these vehicles would likely be tested for CAFE purposes. The only increase in burden with this proposal would be due to a shift when these designs are tested, causing a very slight test load increase prior to model introduction.

C. Relabeling

Under the existing fuel economy label regulations, label values, once calculated, are not changed for the entire model year. Design changes can, however, be implemented after the label has been calculated which may significantly change the fuel efficiency of the vehicles. Design changes after production has started are called running changes. Because label values are only calculated once during a model year, any change in the fuel efficiency caused by design changes is currently not reflected in the label values. Furthermore, since the label value represents the sales weighted average fuel economy prediction for the included designs, changes in sales predictions can significantly affect the estimated fuel economy. These deficiencies in the current calculation procedures adversely affect the representativeness of the label values and thus their usefulness to consumers.

Ideally, label values would be kept most up-to-date by requiring them to be recalculated every time a running change is submitted or a sales shift occurs. However, EPA recognizes the practical limits of reflecting these changes on a continuous basis. Therefore, EPA is proposing two updating mechanisms: A continuous check on label values triggered only by certain design changes, and a single mid-year recalculation for all labels. EPA believes this combination can approximate the ideal system with much less burden on the industry.

While this proposal details a particular combination of update requirements, EPA recognizes that there may be other combinations or single update systems that would achieve comparable results. EPA requests comments on other ways to solve the label updating problem.

EPA is proposing that the label values be recalculated: (1) Once per model year (in January) for the complete product line, and (2) any time running changes wer made directionally affecting any of the specific parameters of equivalent test weight, axle ratio, or road-load horsepower for vehicles covered by a label. For the mid-year recalculation, any label value decrease of 1.0 mpg or more would have to be reflected on new labels. (Manufacturers could optionally relabel for fuel economy increases.) For recalculations triggered by the running change, if the newly calculated label value were 1.0 mpg or more below the city or highway value new labels would be required. A brief explanation of each of these types of relabeling follows:

1. *Mid-Year Recalculations.* Recent experience in the fuel economy program indicates that compared to current label values (calculated early in the model year, often before production starts), the label values that would be calculated using end-of-year data were as much as 3 mpg different for the city value and 4 mpg different for the highway value. Further, 20 percent of the city label values for cars were overstated by 1 mpg or more and 30 percent of the highway label values were overstated by 1 mpg or more.

EPA proposes that manufacturers recalculate all label values using total model year projected sales updated as of December 31 of the calendar year preceding the model year. If any recalculated city *or* highway label value is less than the existing label by 1.0 mpg or more, new label values would have to be in place by the following February 1. All manufacturer-calculated label values (and data used in the calculations) would be submitted to EPA at least five days before implementation. For the recalculation, all base levels would be represented by data from at least the highest projected sales configuration, as with the initial labels. EPA would provide comparable vehicle range values for the labels at an appropriate time before February 1. As is currently required, these updated range values would be incorporated on the labels within 15 days of the date EPA made them available.

The date for the mid-year relabeling was chosen so as to have the least impact on industry resources. The current labeling procedures require that the range of fuel economy of comparable vehicles contained on the labels (but not the label values) be updated (around this time) and these new labels be affixed to subsequent production. Because manufacturers are already required to put new labels on much of their product lines at this time, the only new cost involved would be in performing the calculation and updating sales projections. EPA estimates this cost to be approximately $380,000 for the industry. EPA requests information on other possible costs associated with relabeling, such as for updating advertising and brochures.

EPA acknowledges that if all of manufacturers' advertising had to be altered at mid-model year to reflect revised fuel economy estimates, it would amount to significant disruption in advertising, with possibly higher costs. However, it is likely that the current portion of overstated label values would

be significantly less because of the incentive for manufacturers not to make changes during the year that decrease fuel economy. This incentive would be reinforced by the proposal to require labeling for certain design changes (see below) at any time during the model year. Further, manufacturers' advertising typically centers only on the highest fuel economy model type within a car line, which further decreases the likelihood of label value changes that would affect advertising. Thus, EPA believes that the actual impact of relabeling on advertising cost would not be significant, primarily due to the presence of the relabeling requirements themselves. The risk of affecting advertising would discourage unnecessary design changes that decrease fuel economy.

2. Recalculation Resulting Directly from Design Changes. Certification records show that in the 1982 model year, 115 of the over 800 design changes involved changes in axles, equivalent test weight or road-load horsepower. Because design changes involving any one of these three vehicle characteristics may have a significant effect on fuel economy,[8] EPA is proposing that the label values be immediately recalculated and relabeled, if necessary, to reflect these types of design changes if they are in the direction of decreasing fuel economy. These are specific design changes that are closely controlled by the manufacturer's product planning and, therefore, manufacturers should be responsible for reflecting them in fuel economy estimates to the public.

Specifically, this proposal would require that: (1) Anytime an axle ratio is added which is numerically 10 percent larger than the largest axle ratio tested, or (2) a higher equivalent test weight is added, or (3) when the road-load horsepower is increased by 10 percent (either cumulative or a single change), the label values must be recalculated. If the recalculation, using undated projected annual sales, results in any label calculation reduction of a full 1.0 mpg or more of the city or highway calculation, the affected vehicles would have to be relabeled. (Each manufacturer would have the option to relabel for fuel economy increases by 1.0 mpg or more.) The 1.0 mpg city or highway change in fuel economy was selected to ensure that only those design changes which had a significant effect on fuel economy would trigger a relabeling. That is, changes of less than 1.0 mpg may result in label values changing due to round-off. However, labels will not be revised in these cases.

If the manufacturer were required to relabel based on the above criteria, the new labels would have to be installed on the affected model types at the time the running change was implemented. The manufacturer would submit the new label values, along with the data used in the calculations, to EPA at least five working days before implementations. As is the current practice when new labels are calculated during the year, EPA will supply the manufacturer with the latest available comparable vehicle range values to be used on the new labels.

Current fuel economy regulations do not require supplementary data for changes only in road-load horsepower or increase in equivalent test weight. Therefore, EPA is also proposing that manufacturers be required to submit supplementary fuel economy data for running changes that affect these parameters as described above. EPA does not anticipate that this requirement would significantly increase testing since emissions regulations often require test data for such changes.

3. Gas Guzzler Tax Liability. Currently, a manufacturer's liability for Gas Guzzler Tax on a particular vehicle is determined by the model type fuel economy value that EPA assigns to it. Since the proposed labeling program will cause label values to be updated, EPA proposes that the Gas Guzzler Tax liability be reevaluated whenever a label is updated. This would permit a manufacturer to remove a vehicle from the Gas Guzzler category (or decrease the tax liability) by making fuel economy improvements during the year. The converse would also be true as vehicles could fall into the Gas Guzzler category if model type fuel economy estimates decreased during the model year.

D. Modifications to the Label Information

1. Inclusion of City and Highway Estimates. The fuel economy label currently contains a single fuel economy value referred to as the EPA estimated fuel economy. The EPA estimated fuel economy is based on a test procedure which simulates the relative low speed stop-and-go driving typical in a city or urban environment. Since the current label fuel economy value is based on a city-type test, it does not reflect highway fuel economy performance. This lack of label information about highway fuel economy is particularly significant due to the many improved designs available today (such as overdrive transmission gearing) that mainly affect the highway fuel economy, not city fuel economy. In addition, highway estimates are used and emphasized by manufacturers in their advertising even though they do not appear on the label.

EPA propose a two-number label that would present separate city and highway estimates. Manufacturers' comments on the ANPRM have indicated agreement with this system. The advantage of this two-number system is that individual buyers would determine the expected fuel economy under the driving mode or modes of particular interest to them.

EPA had previously included highway fuel economy estimates on labels during the 1975 through 1978 model years. We subsequently dropped the highway estimate from the labels and termed the former "city" estimate simply as the "estimate." This was done as an interim measure while a solution to the in-use fuel economy shortfall problem could be found. If EPA adopts the previously described shortfall adjustments to label values, the separate city and highway estimates will become more valid and useful. The Agency does not intend to adopt this two-mode label system if shortfall adjustments are not adopted.

2. Elimination of Prior Approvals for Label Values. Current regulations require that manufacturers obtain EPA approval of label values before they can be used. This approval process requires significant EPA resources and can cause delays for manufacturers in labeling vehicles in production.

EPA proposes to eliminate the requirement for prior label approvals. Manufacturers would be responsible for calculating label values and could apply them at their discretion provided they had submitted the label value and supporting calculation to EPA. EPA would retain the function of auditing label calculations at its discretion. If EPA audits revealed vehicles mislabeled too high, manufacturers would be required to relabel the vehicles. Manufacturers would have 15 calendar days to change labels on unsold vehicles and begin installing correct labels on all unlabeled vehicles. The relabeling cost and disruption to advertising should be sufficient incentive for manufacturers to maintain good internal quality control of their label calculations. Thus, no additional mislabeling penalty is proposed. As in running change label updates, EPA would provide the latest available comparable range to be used.

3. Unique Labels for Fuel Efficient Vehicles. Currently, each model type classification (as defined by car line name, basic engine, and transmission class) is represented by a single fuel

[8] EPA Report No. 460/3-80-010, "Passenger Car Fuel Economy: EPA and Road," September 1980, available in Public Docket No. A-80-32.

economy general label value (although labels specific to configurations are allowed temporarily until general labels become available). Manufacturers often have specific fuel efficient design packages within model types that are not appropriately represented by the model type general label value. There is currently no formal mechanism that allows manufacturers to separately label and advertise these fuel efficient packages if they fall within a currently defined model type. EPA agrees that the highlighting of specific fuel efficient designs that are available is consistent with the Agency's goal to provide consumers with accurate fuel economy information. Therefore, EPA proposes to allow manufacturers to separately label specific vehicle designs based on fuel economy performance, providing these vehicles bear a unique name for consumer identification, and providing certain minimum testing requirements are met.

Under this proposal, the manufacturer would be allowed to create unique car lines representing model types separated from the original model types. The new car line name must be different form the remaining car line name (although the unique car line name may be a derivative of the original name, such as Omni Miser), and must appear on the label and on each vehicle bearing the label. For label calculation purposes, the vehicles separated from the original model type will be considered separate basic engines. No subconfiguration may be represented in more than one basic engine, and *all* subconfigurations within a unique label calculation must be represented by test data. The label values for the unique model types contained in the new basic engines would be calculated using existing procedures.

The manufacturer may make unique label subconfiguration groupings as large or small as it desires as long as each subconfiguration in the grouping is represented by test data. Further, the lable updating provisions of this proposal would apply as with other model types.

4. *Clarification and Standardization of Label Format.* Under the current regulations, prior approval of labels encompasses the format as well as the information contained on the label. This approval process costs both the manufacturers and EPA time and resources. Format variation also makes it difficult for potential buyers to locate and understand the information and reduces the usefulness of the label for comparative shopping.

We are proposing changes affecting both the information EPA required on the label and the format itself in order to achieve a certain degree of standardization, improved clarity, and a more streamlined administrative process. The proposed changes to the label format are to establish a standard format and to delete the requirement that EPA approve the label format.

EPA has contracted with a media consultant firm to review specific label formats and provide comments and suggestions.[6] The Department of Energy (DOE) has done similar studies.[7] Drawing from this information and from EPA's experience with various formats used by manufacturers, EPA is presenting two alternatives in this proposal. The format adopted in the final rule will be based on the comments received on these alternatives. Examples of the alternative formats are appended to the regulations.

The first alternative (developed by EPA) allows the manufacturer some flexibility in the information that can be included on the label beyond the minimum information required. It has certain minimum dimensional requirements and must leave at least 60 percent of the label area for the fuel economy values which also have minimum dimensional requirements. This alternative format is presented in the text of the regulations for this NPRM since it allows more variation and, therefore, needs a more detailed description. The second alternative is the fixed format developed by DOE which features a depiction of a gas pump and exact label language. For this alternative, no variations may be made to the exact format except that the size (with contents) may be proportionately increased from minimum dimensions.

EPA also proposes to eliminate the requirement for EPA prior approval of label formats even though some format variation may still be allowed. EPA would instead audit label formats as necessary and could require relabeling if violations occur.

EPA requests comments on the proposed labeling format changes, particularly on:

a. The preferred format alternative;

b. Implementation costs and problems;

c. Consumer information needs and understanding;

d. Advertising guidelines for all media; and

e. Any other proposed systems, including their advantages and disadvantages.

E. Proposed Technical Amendments To Cut Costs and Improve the Data Base

1. Elimination of the Preliminary CAFE Calculation. There are two basic uses of the preliminary CAFE in the current program. One is to provide the manufacturer an early estimate of what the final CAFE could be. A second purpose is to establish the subdivisions of a product line which will be the basis for establishing test requirements for the final CAFE data base. The need for the preliminary CAFE is now being questioned by both EPA and the industry.

EPA originally incorporated the preliminary CAFE concept in response to manufacturers' requests.[8] According to manufacturers, this early program of EPA-confirmed corporate fuel economy values would provide a very good indication of what the final CAFE values would be if no significant changes were introduced by the manufacturers and the projected sales remained stable. They also felt EPA-confirmed values would provide their marketing departments latitude in making marketing decisions if preliminary CAFE's were above the standard. Even though EPA offers the preliminary CAFE as an early indicator of the manufacturer's status for CAFE compliance, in recent years manufacturers seem to have stopped relying on the preliminary CAFE for this purpose. Whether the manufacturer needs it or not, EPA and the manufacturer still must devote resources to generate and confirm the value since this is required by the current regulations.

EPA proposes to eliminate the preliminary CAFE calculation from the fuel economy program. In its place, the regulations would require that the final CAFE include test data on vehicle configurations with total production of 90 percent or more of the manufacturer's total production. If this proposal to eliminate the preliminary CAFE is adopted, manufacturers will be free to choose, in most cases, which designs to test as long as the final CAFE data base represents 90 percent or more of vehicle configuration production. (There would be no change in the existing requirement that all data submitted during the label calculation procedures must also be included in the CAFE calculation and this would also apply to data submitted for relabeling purposes.)

[6] Buckheim & Rowland, Inc., "Fuel Economy Label Design Evaluation," May 1981. Available in Public Docket No. A-80-32.

[7] Pirkey, McNutt, "Consumer Response to Fuel Economy Information—Alternative Sources, Users, and Formats," SAE No. 820792, June 1982, available in Public Docket No. A-80-32

[8] 41 FR 38647, September 10, 1976.

Also related to the preliminary CAFE calculation, under the current regulations (40 CFR 600.507–79(a) (1)), manufacturers may request exemptions from the requirement that supplementary fuel economy data be submitted for running changes based upon preliminary CAFE values. If a manufacturer's preliminary CAFE is sufficiently above the model year's CAFE value, the manufacturer may request such an exemption. Since the exemption decision relies on the preliminary CAFE and since the manufacturers will, in most cases, be free to choose which data to include in the final CAFE data base, EPA proposes that the exemption be eliminated in conjunction with eliminating the preliminary CAFE calculation. Also, in some cases the additional running change data will be needed under the relabeling proposal.

2. *Fuel Economy Adjustments for High Mileage Test Vehicles.* Presently, the regulations allow a maximum mileage accumulation of 10,000 miles for fuel economy data vehicles. This is allowed in order to extend the usefulness of fuel economy test vehicles so that each vehicle can be used for more tests, thus saving the cost of new test vehicles. It also allows vehicles which had been used to generate emission certification data under 40 CFR Part 86 to be reconfigured and used as fuel economy data vehicles.

Fuel economy levels usually improve with mileage accumulation because engine wear reduces friction. Test vehicle mileage over 4,000 miles can consequently bias fuel economy test results from the original 4,000-mile base. EPA conducted an analysis (available in the public docket) of fuel economy data from 1976 through 1981 model year test vehicles.* Average fuel economy improvements of approximately 5 percent were calculated between 4,000 and 10,000 miles. Thus, for example, by increasing the mileage accumulated on a test vehicle to 10,000 miles, fuel economy can be increased on the average by about 1.0 mpg on a vehicle which has a 4,000-mile fuel economy of 20 mpg. In the 1976 model year, approximately 8 percent of the fuel economy tests were performed on vehicles which had accumulated over 6,200 miles. By the 1980 model year, 35 percent of the tests were performed on vehicles which had accumulated over 6,200 miles. This increased use of test vehicles which have accumulated high mileage tends to bias the fuel economy data.

EPA is proposing (for labeling only) to apply an adjustment factor to test data from vehicles which exceed 6,200 miles (10,000 kilometers). This would allow manufacturers to continue using existing test vehicles, but the fuel economy bias caused by higher mileage would be eliminated. An adjustment equation is contained in the test of the proposed regulation. This proposal would allow the manufacturer to test vehicles with up to 6,200 miles accumulation without a factor being applied to the fuel economy results. For any tests conducted on vehicles with 6,200 miles or more, and up to 10,000 miles, the test results must be adjusted to 4,000-mile levels. The proposed method would allow manufacturers to choose between the use of the adjustment factors for vehicles over 6,200 miles or testing a new vehicle.

Because the proposal is to adjust the fuel economy of vehicles exceeding 6,200 miles back to a 4,000-mile reference point, we recognize that it would constitute a strong disincentive to accumulate more than 6,200 miles on a test vehicle. That disincentive is intended without going so far as to establish an absolute prohibition. Recent changes to the emission certification regulations (46 FR 50464, October 13, 1981) have created greater flexibility to reconfigure vehicles and to perform the emission certification tests sooner than 4,000 miles. This leaves sufficient latitude to reconfigure these vehicles again and fulfill any necessary fuel economy data requirements without accumulating over 6,200 miles. We believe the tendency to accumulate over 6,200 miles is not driven by a desire to save costs by maximizing vehicle reuse but by the desire to generate the maximum fuel economy possible within the time and resources available to the manufacturer to accumulate mileage. This creates inequity in the comparability of fuel economy values and favors manufacturers who have resources available to accumulate additional mileage.

This proposal to adjust data on vehicles with mileage over 6,200 miles only applies to fuel economy values used for label calculations. Since this rulemaking is not intended to affect CAFE stringency, we are not proposing now to use the adjusted values in the CAFE calculation.

3. *Drivetrain Separation.* a. Presently, the definition of "transmission class" does not explicitly distinguish between front- and rear-wheel drive. Consequently, either front- or rear-wheel drive vehicles, or a combination of both, can generate fuel economy data to represent a base level. Available EPA test data show that, in general, configurations tested with rear-wheel drive achieve better tested fuel economy than the same configurations tested with front-wheel drive. This difference in testing results can compromise the representativeness of particular fuel economy values.

The current fuel economy regulations (40 CFR 600.002–79(a)(22)) allow the Administrator to separate vehicles with front- and rear-wheel drive systems into separate transmission classes based on "other characteristics determined significant by the Administrator," and thus, into separate base levels. EPA began separating front- and rear-wheel drive transmission vehicles into separate transmission classes in the 1981 model year using this provision. EPA proposes in this NPRM to make this separation explicit in the regulations.

b. Some manufacturers are now installing automatic transmissions that have "lockup" torque converters and have also installed transmissions with "overdrive" gear ratios. Both of these features improve the fuel efficiency of the vehicle.

EPA proposes that both overdrive gearing and automatic transmission with lockup be explicitly included in the definition of transmission class. Thus, consumers would be notified of the fuel economy impact (since transmission class determines a model type) and the manufacturer would get fulll credit for these features by having them calculated and listed separately both in the *Guide* and on vehicle labels. Few, if any, additional tests would be required by this change.

4. *Interior Volume.* EPA uses the interior volume of vehicles to classify passenger automobiles to aid the consumer in comparing the fuel efficiency of similar vehicles. The current classification technique was published as a final rule in the September 12, 1977 **Federal Register** (42 FR 45668).

EPA is proposing three changes to the current method for measuring vehicles to account for: (1) The cargo volume of hatchbacks and station wagons, (2) the total front-seat leg room, and (3) adding interior volume measurements to the two-seater vehicle classification. Since these changes will result in new interior volumes for all vehicles, some of the vehicles could be in a new interior volume classification. Therefore, EPA is requesting that manufacturers include in their comments interior volume information on these vehicles that would change classification. This

*EPA Report No. EPA/AA/CPSB/81–03, "Effect of Vehicle Mileage on Tested Fuel Economy," February 1981.

information will be used to determine whether the existing ranges need to be adjusted.

5. *Reduced Reporting Requirements.* EPA proposes to reduce the manufacturers' reporting burdens by eliminating requirements to submit certain information to EPA and to require that information be retained by the manufacturer. This information concerns test vehicle calibrations and maintenance records, and also incudes certain interior volume calculation information. Since EPA does not routinely use this information, it no longer needs to be submitted. However, under this proposal, the manufacturer would have to make these records available to EPA upon request.

III. Other Major Alternatives Considered

In this effort to improve the credibility and usefulness of EPA's fuel economy information, EPA considered many alternatives. The most significant alternatives considered for each of the proposed modifications to the existing regulations are outlined below.

A. Changes in the Test Procedure

A logical option to bring EPA estimates more in line with in-use experience is to make the fuel economy test procedure more closely match actual in-use conditions. However, in order to minimize test costs and maximize the usefulness of the data, test procedures should be the same for the fuel economy labeling program and the manufacturer's CAFE compliance program. Furthermore, when Congress established mandatory CAFE standards, they were based on then-current test procedures. If changes to the basic test cycle would significantly affect the stringency of the CAFE standards, adjusting the standards or test results might be necessary to maintain the same relative stringency. Additionally, a large portion of the fuel economy data are derived from emissions tests since EPA uses the same urban test cycle for both emissions and fuel economy. Changing the test cycle for fuel economy labeling purposes only would double the testing costs to obtain fuel economy data on emission-data vehicles. Finally, major test procedure changes would require costly capital equipment investments and would require at least five years to develop and implement, thus delaying for several years the implementation of an improved fuel economy labeling program.

B. Estimated Fuel Economy Ranges

For each model type, EPA could determine a range of fuel economy based on the estimated percentage of drivers which would achieve fuel economy within the range. EPA could establish a highly inclusive range that would allow, for example, 90 percent of drivers to achieve values within the range but then the range could be so wide as to be meaningless to consumers. Alternatively, EPA could establish a less inclusive fuel economy range that would be more useful for comparisons, but a large number of people would get fuel economy outside of the range. The range approach could make people satisfied that they achieve fuel economy within the limits expected. However, it would not help in comparison shopping since consumers would not know where within the range their fuel economy would most likely be. People might also continue to perceive the range limits as a city value and a highway value, but these range limits may not be the most accurate estimates of expected average in-use city and highway fuel economy.

C. Use of Combined Number Only

EPA considered replacing the existing estimated EPA number with another single number representing a combined city and highway fuel economy value (55 percent city and 45 percent highway weighting). The combined figure would have been a harmonic average of the city and highway values. One of the major problems with this approach is that few drivers actually operate their vehicles with this proportion of driving and while the number might provide for an easy way to comparison shop it would probably not reflect in-use fuel economy. ANPRM commenters did not support this approach.

D. Technology-Specific Adjustment Factors

EPA conducted a thorough analysis of alternatives for developing separate shortfall adjustment factors for different engine/drivetrain designs.[10] Such an approach would probably be more technically correct than applying uniform adjustments across vehicle designs because some design characteristics have been found to exhibit different relationships between laboratory results and on-road results. However, the analysis of how to categorize designs and assign them adjustment factors is very complex and requires an enormous (as well as complete and up-to-date) data base of in-use results. EPA has derived technology-specific adjustment factors based on currently available data, but in-use data are lacking for light-duty trucks and for some of the more recent designs such as light-duty diesels and some front-wheel drive technology. Although EPA considered proposing technologies-specific factors, the potential controversy over the validity and fairness of these factors led EPA to opt for the uniform factors as an initial step. Another disadvantage of technology-specific factors is that we believe technology changes would require frequent update of the factors. Simple uniform factors may also need to be updated, but since their use would not change the competitive ranking order of vehicle label values and since the factors would be based upon the overall average shortfall of all technology types, they should require less frequent updating. This would result in less disruption to manufacturers' planning and marketing practices and less resource expenditures needed by EPA to run a continuous factors updating program. EPA requests comments on the technology-specific analyses and how (or if) EPA should pursue the development of technology-specific factors in the future.

E. Design Factor Label Calculations

EPA considered using design adjustment factors to predict fuel economy mathematically for each untested subconfiguration. This would have reduced significantly the bais in the label fuel economy caused by lack of data on the configurations included within the model type covered by the labels. It can also improve the representation of the label values and possibly reduce testing requirements for both the label calculation requirements and CAFE requirements. (The development and impact analysis of this system is contained in EPA Report No. EPA–AA–CPSB–81–02 entitled, "A Comparison of Current and Proposed Labeling Programs," and is available in the public docket.) Several manufacturers have indicated, however, that in order to "prove out" the adjustment equations they would also have to test vehicles to compare tested to calculated results. This method would also tend to be more complex to set up initially and might cause some concern as to the validity of "calculating" test results.

We have concluded that only a small percentage of labels [11] are overstated by

[10] EPA Report No. EPA/AA/CTAB/FE–82–6, "Analysis of In-Use Fuel Economy Data: Stage I," Dillard Murrell, September, 1982, available in Public Docket No. A–80–83.

[11] For passenger cars only three percent of the city labels and nine percent of the highway values appear overstated by two or more mpg and for light-duty trucks only one percent of the city labels and six percent of the highway labels appear overstated by two or more mpg.

two mpg or more due to lack of data and deficiencies in the current data aggregation system. The implementation of a new system as complex as the design factor approach would seem to be a drastic solution relative to the magnitude of the problem. Hence, we have proposed the simpler approach of requiring the testing of the highest sales volume in each configuration as the minimum data requirement to generate a label. We believe this approach will correct the large majority of overstated labels with the minimum change to the current system. EPA welcomes comments on this approach for labeling as well as comments as to whether EPA should consider the use of design factoring in generating analytical CAFE data (as is currently allowed in the regulations).

F. Labels That Are More Design Specific

EPA indicated in the ANPRM that it was considering label values for subgroups within each model type. The level of detail could have been as detailed as the subconfiguration level. Comments received to this advanced notice indicated that labeling at this level would be very costly. This high cost would result because most manufacturers apparently do not have a mechanism for tracking such unique vehicle designs during the assembly process. Therefore, to set up this tracking mechanism to ensure that each vehicle is properly labeled, complicated and very costly systems would have to be purchased and installed. EPA also considered less detailed levels of labeling (such as by axle ratio) which would have resulted in an improvement for vehicle comparisons. However, these would have required that more vehicles be tested early in the model year or that design factors be used for estimating test results. EPA requests comments on whether such approaches should still be considered to improve the labeling program.

IV. Cost of Implementation

EPA has estimated, based on information from previous model years, the likely cost to maufacturers of the changes proposed in this NPRM. The proposed changes are estimated to cost the entire industry less than $600,000 per year. A detailed analysis of the likely costs of the proposals in this NPRM is contained in a document entitled "Cost Analysis of Proposed Changes to 40 CFR Part 600 to Improve Fuel Economy Labeling and the Fuel Economy Data Base," which can be obtained from Public Docket No. A–80–32. EPA invites comments and additional information to improve the accuracy of the analysis used to develop the final rule.

V. EPCA Constraints

Section 503(d)(1) of EPCA, 15 U.S.C. 2003(b)(1), requires that for purposes of CAFE, fuel economy be measured and calculated by procedures established by the EPA Administrator. It further requires that "Procedures so established with respect to passenger automobiles (other than for purposes of Section 506) shall be procedures utilized by the EPA Administrator for model year 1975 (weighted 55 percent urban cycle and 45 percent highway cycle) or procedures which yield comparable results." The data base improvements EPA is proposing in this notice (see Section II.E of this preamble) are intended to improve the completeness and representativeness of the fuel economy data base so that EPA fuel ecomony estimates do not overstate fuel economy improvements as compared to the 1975 base model year. These options would not change the 1975 testing or CAFE calculation procedures themselves, but would only require that manufacturers use more representative data.

Section 503(d)(3), 15 U.S.C. 2003(d)(3), of EPCA states, "testing and calculation procedures applicable to a model year, and any amendment to such procedures (other than a technical or clerical amendment), shall be promulgated not less than 12 months prior to the model year to which such procedures apply." EPA believes that the changes proposed in this NPRM are technical amendments to procedures under Section 503(d)(3) of EPCA. They would change neither the actual fuel economy testing procedures nor the basic formula used to derive manufacturers' corporate average fuel economy levels and would not entail practical leadtime constraints or compliance burdens for manufacturers.

These proposed rules are technical changes to existing requirements intended to improve the completeness and representativeness of the data base. Changes of this nature, which do not require (as a practical matter) a year's leadtime, are the type of changes Congress had in mind when it created the exception to the leadtime requirements of Section 503(d)(3). Changes to the labeling program are generally not constrained by the leadtime requirements of Section 503(d)(3). However, the Agency invites comments on the question of whether or not the changes proposed here should be treated as technical amendments.

VI. Regulatory Analysis

Under Executive Order 12291, EPA must judge whether a regulation is "major" and therefore subject to the requirement of a regulatory impact analysis. This regulation is not major because it will result in an annual effect on the economy of less than $100 million. Also, this regulation should not result in increased costs or prices for consumers, industries, or others, nor should it have adverse effects on competition, employment, investment, or productivity.

This action was submitted to the Office of Management and Budget for review as required by Executive Order 12291. Any comments from OMB to EPA and any EPA response to those comments are available for public inspection in the docket for this rulemaking: Docket No. A–80–32. The EPA's Central Docket Section (A–130) is located at 401 M Street SW., Washington, D.C. 20460.

VII. Reporting and Recordkeeping Requirements

These amendments would require the manufacturers to maintain additional records on the recalculation of label values and the approved test data used to generate them. However, the reporting of the additional label calculations would be minor compared to existing requirements. When coupled with the decrease in reporting burden due to the elimination of test vehicle calibration specification, label format, and preliminary CAFE approvals, the total program reporting and recordkeeping burden would probably decrease. Furthermore, the proposed flexibility for manufacturers to issue their own labels, rather than wait for EPA to process them, while not reducing reporting or recordkeeping requirements, should reduce manufacturers' operating costs due to their greater control over their own schedules.

Reporting, recordkeeping and labeling requirements in 40 CFR Part 600 have previously been approved by OMB and assigned control number 2000–0390. The modifications proposed in this notice have been submitted for approval to OMB under section 3504(h) of the Paperwork Reduction Act of 1980, U.S.C. 4501 *et seq.* Comments on information collection requirements proposed in this notice should be directed to the Office of Information and Regulatory Affairs, OMB, ATTN: Desk Officer EPA.

VIII. Regulatory Flexibility Act

Under the Regulatory Flexibility Act, 5 U.S.C. 601 *et seq.*, EPA is required to determine whether a regulation will have a significant economic impact on a substantial number of small entities so

as to require a regulatory analysis. The revision of the fuel economy regulation established by this rulemaking should reduce the burden, including costs of compliance with fuel economy requirements for small entities. Therefore, pursuant to 5 U.S.C. 605(b), I hereby certify that this rule will not have a significant economic impact on a substantial number of small entities.

IX. List of Subjects in 40 CFR Part 600

Electric power, Energy conservation, Gasoline, Labeling, Motor vehicles, Reporting and recordkeeping requirements, Administrative practice and procedure, Fuel economy.

Dated: May 24, 1983.

William D. Ruckelshaus,

Administrator.

PART 600—[AMENDED]

For the reasons set forth in the preamble, 40 Part 600 is amended as follows:

1. The authority for Part 600 reads as follows:

Authority: Title III of the Energy Policy and Conservation Act of 1975, Pub. L. 94-163, 89 Stat. 871, Title IV of the National Energy Conservation Policy Act of 1978, Pub. L. 95-619, 92 Stat. 3206.

2. A new § 600.002-85 is added to read as follows:

§ 600.002-85 Definitions.

(a) As used in this subpart, all terms not defined herein shall have the meaning given them in the Act:

(1) "Act" means Part I of Title V of the Motor Vehicle Information and Cost Savings Act (15 U.S.C. 1901 et seq.).

(2) "Administrator" means the Adminstrator of the Environmental Protection Agency or his authorized representative.

(3) "Secretary" means the Secretary of Transportation or his authorized representative.

(4) "Automobile" means any four-wheel vehicle propelled by a combustion engine using onboard fuel or by an electric motor drawing current from rechargeable storage batteries or other portable energy storage devices (rechargeable using energy from a source off the vehicle such as residential electric service) which is manufactured primarily for use on public streets, roads, or highways (except any vehicle operated on a rail or rails) and which is rated at 8,500 pounds gross vehicle weight or less or is a type of vehicle which the Secretary determines is substantially used for the same purposes.

(5) "Passenger Automobile" means any automobile which the Secretary determines is manufactured primarily for use in the transportation of no more than 10 individuals.

(6) "Model Year" means the manufacturer's annual production period (as determined by the Administrator) which includes January 1 of such calendar year. If a manufacturer has no annual production period, the term "model year" means the calendar year.

(7) "Federal Emission Test Procedure" refers to the dynamometer driving schedule, dynamometer procedure, and sampling and analytical procedures described in Part 86 for the respective model year, which are used to derive city fuel economy data for gasoline-fueled or diesel vehicles.

(8) "Federal Highway Fuel Economy Test Procedure" refers to the dynamometer driving schedule, dynamometer procedure, and sampling and analytical procedures described in Subpart B of this part and which are used to derive highway fuel economy data for gasoline-fueled or diesel vehicles.

(9) "Fuel" means: (i) Gasoline and diesel fuel for gasoline- or diesel-powered automobiles or (ii) electrical energy for electrically powered automobiles.

(10) "Fuel Economy" means: (i) The average number of miles traveled by an automobile or group of automobiles per gallon of gasoline or diesel fuel consumed as computed in § 600.113 or § 600.207 or (ii) the equivalent petroleum-based fuel economy for an electrically powered automobile as determined by the Secretary of Energy.

(11) "City Fuel Economy" means the fuel economy determined by operating a vehicle (or vehicles) over the driving schedule in the Federal emission test procedure.

(12) "Highway Fuel Economy" means the fuel economy determined by operating a vehicle (or vehicles) over the driving schedule in the Federal highway fuel economy test procedure.

(13) "Combined Fuel Economy" means the fuel economy value determined for a vehicle (or vehicles) by harmonically averaging the city and highway fuel economy values, weighted 0.55 and 0.45 respectively, for gasoline-fueled and diesel vehicles. For electric vehicles, the term means the equivalent petroleum-based fuel economy value as determined by the calculation procedure promulgated by the Secretary of Energy.

(14) "Average Fuel Economy" means the unique fuel economy value as computed under § 600.510 for a specific class of automobiles produced by a manufacturer that is subject to average fuel economy standards.

(15) "Certification Vehicle" means a vehicle which is selected under § 86.084-24(b)(1) and used to determine compliance under § 86.084-30 for issuance of an original certificate of conformity.

(16) "Fuel Economy Data Vehicle" means a vehicle used for the purpose of determining fuel economy which is not a certification vehicle.

(17) "Label" means a sticker that contains fuel economy information and is affixed to new automobiles in accordance with Subpart D of this part.

(18) "Dealer" means a person who resides or is located in the United States, any territory of the United States, or the District of Columbia and who is engaged in the sale or distribution of new automobiles to the ultimate purchaser.

(19) "Model Type" means a unique combination of car line, basic engine, and transmission class

(20) "Car Line" means a name denoting a group of vehicles within a make or car division which has a degree of commonality in construction (e.g., body, chassis). Car line does not consider any level of decor or opulence and is not generally distinguished by characteristics as roof line, number of doors, seats, or windows except for station wagons or light-duty trucks. Station wagons and light-duty trucks are considered to be different car lines than passenger cars.

(21) "Basic Engine" means a unique combination of manufacturer, engine displacement, number of cylinders, fuel system (as distinguished by number of carburetor barrels or use of fuel injection), catalyst usage, and other engine and emission control system characteristics specified by the Administrator. For electric vehicles, basic engine means a unique combination of manufacturer and electric traction motor, motor controller, battery configuration, electrical charging system, energy storage device, and other components as specified by the Administrator.

(22) "Transmission Class" means a group of transmissions having the following common features: basic transmission type (manual, automatic, or semi-automatic), number of forward gears used in fuel economy testing (e.g., manual four-speed, three-speed automatic, two-speed semi-automatic), drive system (e.g., front-wheel-drive, all-wheel-drive), type of overdrive, if applicable (e.g., final gear ratio less than 1.00, separate overdrive unit), torque converter type, if applicable (e.g., non-lockup, lockup, variable ratio), and other transmission characteristics that may be

determined to be significant by the Administrator.

(23) "Base Level" means a unique combination of basic engine inertia weight class and transmission class.

(24) "Vehicle Configuration" means a unique combination of basic engine, engine code, inertia weight class, transmission configuration, and axle ratio within a base level.

(25) "Engine Code" means, for gaoline-fueled and diesel vehicles, a unique combination, within an engine-system combination (as defined in Part 86 of this chapter), of displacement, carburetor (or fuel injection) calibration, distributor calibration, choke calibration, and auxiliary emission control devices, and other engine and emission control system components specified by the Administrator. For electric vehicles, engine code means a unique combination of manufacturer, electric traction motor, motor configuration, motor controller, and energy storage device.

(26) "Inertia Weight Class" means the class, which is a group of test weights, into which a vehicle is grouped based on its loaded vehicle weight in accordance with the provisions of Part 86.

(27) "Transmission Configuration" means a unique combination, within a transmission class, of the total number of forward gears. If the Administrator determines that sufficient fuel economy differences exist within a transmission configuration the Administrator may further subdivide that configuration by such features as gear ratios, torque converter multiplication ratio, stall speed, shift calibration, or shift speed.

(28) "Axle Ratio" means the number of times the input shaft to the differential (or equivalent) turns for each turn of the drive wheels.

(29) "Auxiliary Emission Control Device (AECD)" means an element of design as defined in Part 86.

(30) "Rounded" means a number shortened to the specific number of decimal places in accordance with the "Round Off Method" specified in ASTM E 29-67.

(31) "Calibration" means the set of specifications, including tolerances, unique to a particular design, version of application of a component, or component assembly capable of functionally describing its operation over its working range.

(32) "Production Volume" means, for a domestic manufacturer, the number of vehicle units domestically produced in a particular model year but not exported, and for a foreign manufacturer, means the number of vehicle units of a particular model imported into the United States.

(33) "Body Style" means a level of commonality in vehicle construction as defined by number of doors and roof treatment (e.g., sedan, convertible, fastback, hatchback) and number of seats (i.e., front, second, or third seat) requiring seat belts pursuant to National Highway Traffic Safety Administration safety regulations. Station wagons and light trucks are identified as car lines.

(34) "Hatchback" means a passenger automobile where the conventional luggage compartment, i.e., trunk, is replaced by a cargo area which is open to the passenger compartment and accessed vertically by a rear door which encompasses the rear window.

(35) "Pickup Truck" means a nonpassenger automobile which has a passenger compartment and an open cargo bed.

(36) "Station Wagon" means a passenger automobile with an extended roof line to increase cargo or passenger capacity, cargo compartment open to the passenger compartment, a tailgate, and one or more rear seats readily removed or folded to facilitate cargo carrying.

(37) "Gross Vehicle Weight Rating" means the manufacturer's gross weight rating for the individual vehicle.

(38) "Ultimate Consumer" means the first person who purchases an automobile for purposes other than resale or leases an automobile.

(39) "Van" means any light truck having an integral enclosure fully enclosing the driver compartment and load-carrying device, and having no body sections protruding more than 30 inches ahead of the leading edge of the windshield.

(40) "Base Vehicle" means the lowest priced version of each body style that makes up a car line.

(41) "Nonpassenger Automobile" means an automobile that is not a passenger automobile, as defined by the Secretary of Transportation at 49 CFR 523.5.

(42) "Four-Wheel-Drive General Utility Vehicle" means a four-wheel-drive, general purpose automobile capable of off-highway operation that has a wheelbase not more than 110 inches and that has a body shape similar to a 1977 Jeep CJ-5 or CJ-7, or the 1977 Toyota Land Cruiser, as defined by the Secretary of Transportation at 49 CFR 553.4.

(43) "Test Weight" means the weight within an inertia weight class which is used in the dynamometer testing of a vehicle, and which is based on its loaded vehicle weight in accordance with the provisions of Part 86.

(44) "Secretary of Energy" means the Secretary of Energy or his authorized representative.

(45) "Electric Traction Motor" means an electrically powered motor which provides tractive energy to the wheels of a vehicle.

(46) "Energy Storage Device" means a rechargeable means of storing tractive energy on board a vehicle such as storage batteries or a flywheel.

(47) "Motor Controller" means an electronic or electromechanical device to convert energy stored in an energy storage device into a form suitable to power the traction motor.

(48) "Electrical Charging System" means a device to convert 60Hz alternating electric current, as commonly available in residential electric service in the United States, to a proper form for recharging the energy storage device.

(49) "Battery Configuration" means the electrochemical type, voltage, capacity (in Watt-hours at the c/3 rate), and physical characteristics of the battery used as the tractive energy storage device.

(50) "Drive System" means the number and location of drive axles (e.g., front-wheel-drive, all-wheel-drive, rear-wheel-drive) and any other feature of the drive system if the Administrator determines that such other feature may result in a fuel economy difference.

(51) "Subconfiguration" means a unique combination within a vehicle configuration of equivalent test weight, road-load horsepower, and any other operational characteristic or parameter which the Administrator determines may significantly affect fuel economy within a vehicle configuration.

3. A new § 600.006-85, is added to read as follows.

§ 600.006-85 Data and information requirements for fuel economy vehicles.

(a) For certification vehicles with less than 10,000 miles, the requirements of this section are considered to have been met except as noted in paragraph (c) of this section.

(b)(1) The manufacturer shall submit the following information for each fuel economy data vehicle:

(i) A description of the vehicle, exhaust emission test results, applicable deterioration factors, and adjusted exhaust emission levels.

(ii) A statement of the origin of the vehicle including total mileage accumulation, and modifications (if any) from the vehicle configuration in which the mileage was accumulated. [For modifications requiring advance approval by the Administrator, the name of the Administrator's representative approving the modification and date of approval are required.] If the vehicle

was previously used for testing for compliance with Part 86 of this chapter or previously accepted by the Administrator as a fuel economy data vehicle in a different configuration, the requirements of this paragraph may be satisfied by reference to the vehicle number and previous configuration.

(iii) A statement that the fuel economy data vehicle, with respect to which data are submitted:

(A) Has been tested in accordance with applicable test procedures,

(B) Is, to the best of the manufacturer's knowledge, representative of the vehicle configuration listed, and

(C) Is in compliance with applicable exhaust emission standards.

(2) The manufacturer shall retain the following information for each fuel economy data vehicle, and make them available to the Administrator upon request:

(i) A description of all maintenance to engine, emission control system, or fuel system components performed within 2,000 miles prior to fuel economy testing.

(ii) In the case of electric vehicles, the manufacturer should provide a description of all maintenance to electric motor, motor controller, battery configuration, or other components performed within 2,000 miles prior to fuel economy testing.

(iii) A copy of calibrations for engine, fuel system, and emission control devices, showing the calibration of the actual components on the test vehicle as well as the design tolerances.

(iv) In the case of electric vehicles, the manufacturer should provide a copy of calibrations for the electric motor, motor controller, battery configuration, or other components on the test vehicle as well as the design tolerances.

(v) If calibrations for components in paragraph (b) of this section were submitted previously as part of the description of another vehicle or configuration, the original submittal may be referenced.

(c) The manufacturer shall submit the following fuel economy data:

(1) For vehicles tested to meet the requirements of Part 86 (other than those chosen in accordance with § 86.084–24 (c) and (h)), the city and highway fuel economy results from all tests on that vehicle, and the test results adjusted in accordance with paragraph (g) of this section.

(2) For each fuel economy data vehicle, all individual test results (excluding results of invalid and zero mile tests) and, if the data are used in fuel economy label calculations, the test results adjusted in accordance with paragraph (g) of this section.

(d) The manufacturer shall submit an indication of the intended purpose of the data (e.g., data required by the general labeling program or voluntarily submitted for specific labeling).

(e) In lieu of submitting actual data from a test vehicle, a manufacturer may provide fuel economy values derived from an analytical expression, e.g., regression analysis. In order for fuel economy values derived from analytical methods to be accepted, the expression (form and coefficients) must have been approved by the Administrator.

(f) If, in conducting tests required or authorized by this part, the manufacturer utilizes procedures, equipment, or facilities not described in the Application for Certification required in § 86.084–21, the manufacturer shall submit to the Administrator a description of such procedures, equipment, and facilities.

(g)(i) The manufacturer shall adjust all test data used for fuel economy label calculations generated by vehicles with engine-system combinations with more than 6,200 miles (10,000 kilometers) using either of the following equations:

Equation A

$$FE_{6.400km} = FE_T\,[0.969 + 0.523 \times 10^{-3}\,(km)]^{-1}$$

Equation B

$$FE_{4.000mi} = FE_T\,[0.969 + 0.842 \times 10^{-3}\,(m)]^{-1}$$

Where:

$FE_{6.400km}$ = Fuel economy data adjusted to 6,400-kilometer test point

$FE_{4.000mi}$ = Fuel economy data adjusted to 4,000-mile test point

FE_T = Tested fuel economy value

km = Kilometer accumulation at test point

mi = Miles accumulation at test point

(ii) For vehicles with 6,200 miles (10,000 kilometers) or less accumulated, the manufacturer is not required to adjust the data.

4. A new § 600.010–85 is added to read as follows:

§ 600.010–85 Vehicle test requirements and minimum data requirements.

(a) For each certification vehicle defined in this part, and for each vehicle tested according to the emission test procedures in Part 86 for addition of a model after certification (§ 86.079–32) or, approval of running change (§ 86.079–33):

(1) The manufacturer shall generate city fuel economy data by testing according to the applicable procedures.

(2) The manufacturer shall generate highway fuel economy data by:

(i) Testing according to applicable procedures, or

(ii) Use of an analytical technique as described in § 600.006(e).

(3) The data generated in paragraphs (a) (1) and (2) of this section, shall be submitted to the Administrator in combination with other data for the vehicle required to be submitted in Part 86 of this Title.

(b) For each fuel economy data vehicle:

(1) The manufacturer shall generate city fuel economy data and highway fuel economy data by:

(i) Testing according to applicable procedures, or

(ii) Use of analytical technique as described in § 600.006(e), in addition to testing (e.g., city fuel economy data by testing, highway fuel economy data by analytical technique).

(2) The data generated shall be submitted to the Administrator according to the procedures in § 600.006.

(c) *Minimum data requirements for labeling:* (1) In order to establish initial fuel economy label values under § 600.306, or mid-year label updates under § 600.314(c), the manufacturer shall use only test data accepted in accordance with § 600.008(b) and (f) meeting the minimum coverage of:

(i) Data required for emission certification under §§ 86.082–24, 86.079–32, 86.079–33, and 86.082–34.

(ii) Data from the highest projected model year sales subconfiguration within the highest projected model year sales configuration for each base level, or

(iii) For additional model types established under § 600.207(a)(2), data from each subconfiguration included within the model type.

(2) For the purpose of calculating fuel economy label values for running change updates under § 600.314(b), the manufacturer shall submit data required under § 600.507.

(d) *Minimum data requirements for the manufacturer's average fuel economy:* For the purpose of calculating the manufacturer's average fuel economy under § 600.510, the manufacturer shall submit test data representing at least 90 percent of the manufacturer's actual model year production, by configuration, for each category identified for calculation under § 600.510(a).

5. A new § 600.206–85, is added to read as follows:

§ 600.206–85 Calculation and use of fuel economy values for gasoline-fueled, diesel, and electric vehicle configurations.

(a) Fuel economy values determined for each vehicle and as approved in § 600.008 (b) or (f) are used to determine city, highway, and combined fuel economy values for each vehicle configuration (as determined by the

Administrator) for which data are available.

(1) If only one set of city and highway fuel economy values are accepted for a vehicle configuration, these values, rounded to the nearest tenth of a mile per gallon, comprise the city and highway fuel economy values for that configuration.

(2) If more than one city or highway fuel economy value is accepted for a vehicle configuration:

(i) All data shall be grouped according to the subconfiguration at which the data were generated using sales projections supplied in accordance with § 600.207(a)(3).

(ii) Within each group of data, all values are harmonically averaged and rounded to the nearest 0.0001 of a mile per gallon in order to determine city and highway fuel economy values for each subconfiguration at which the vehicle configuration was tested.

(iii) All city fuel economy values and all highway fuel economy values calculated in paragraph (a)(2)(ii) of this section are (separately for city and highway) averaged in proportion to the sales fraction (rounded to the nearest 0.0001) within the vehicle configuration (as provided to the Administrator by the manufacturer) of vehicles of each tested subconfiguration. The resultant values, rounded to the nearest 0.0001 mile per gallon, are the city and highway fuel economy values for the vehicle configuration.

(3) The combined fuel economy value for a vehicle configuration is calculated by harmonically averaging the city and highway fuel economy values as determined in § 600.206(a) (1) or (2), weighted 0.55 and 0.45 respectively, and rounded to the nearest 0.0001 mile per gallon. A sample of this calculation appears in Appendix II to this part.

(b) If only one equivalent petroleum-based fuel economy value exists for an electric configuration, that value, rounded to the nearest tenth of a mile per gallon, will comprise the petroleum-based fuel economy for that configuration.

(c) If more than one equivalent petroleum-based fuel economy value exists for an electric vehicle configuration, all values for that vehicle configuration are harmonically averaged and rounded to the nearest 0.0001 mile per gallon for that configuration.

6. A new § 600.207–85 is added to read as follows:

§ 600.207–85 Calculation of fuel economy values for a model type.

(a) Fuel economy values for a base level are calculated from vehicle configuration fuel economy values as determined in § 600.206(a) for low-altitude tests.

(1) If the Administrator determines that automobiles intended for sale in the State of California are likely to exhibit significant differences in fuel economy from those intended for sale in other states, he will calculate fuel economy values for each base level for vehicles intended for sale in California and for each base level for vehicles intended for sale in the rest of the states.

(2) In order to highlight the fuel efficiency of certain designs otherwise included within a model type, a manufacturer may wish to subdivide a model type into one or more additional model types. This is accomplished by separating subconfigurations from existing base level(s) and placing them into new base level(s). The new base level(s) are identical to the existing base level(s) except that they shall be considered, for the purposes of this paragraph, as containing a new basic engine. The manufacturer will be permitted to determine such new basic engines and base level(s) if:

(i) Each additional model type subsequently divided has a unique car line name and that name appears on the label and on the vehicle bearing that label, and

(ii) The subconfigurations included in the new base levels are not included in any other base level which differs only by basic engine (i.e., they are not included in the calculation of the orginal base level fuel economy values), and

(iii) All subconfigurations within the new base level(s) are represented by test data in accordance with § 600.010(c)(ii).

(3) The manufacturer shall supply total model year sales projections for each car line/vehicle subconfiguration combination.

(i) Sales projections must be supplied separately for each car line/vehicle subconfiguration intended for sale in California and each car line/vehicle subconfiguration intended for sale in the rest of the states if required by the Administrator under paragraph (a)(1) of this section.

(ii) Manufacturers shall update sales projections at the time any model type value is calculated for a label value.

(iii) The requirements of this paragraph may be satisfied by providing an amended application for certification, as described in § 86.084–21 of this chapter.

(4) Vehicle configuration fuel economy values, as determined in § 600.206(a), are grouped according to base level.

(i) If only one vehicle configuration within a base level has been tested, the fuel economy value from that vehicle configuration constitutes the fuel economy for that base level.

(ii) If more than one vehicle configuration within a base level has been tested, the vehicle configuration fuel economy values are harmonically averaged in proportion to the respective sales fraction (rounded to the nearest 0.0001) of each vehicle configuration and the resultant fuel economy value rounded to the nearest 0.0001 mile per gallon.

(5) The procedure specified in § 600.207(a) will be repeated for each base level, thus establishing city, highway, and combined fuel economy values for each base level.

(6) For the purposes of calculating a base level fuel economy value, if the only vehicle configuration(s) within the base level are vehicle configuration(s) which are intended for sale at high altitude, the Administrator may use fuel economy data from tests conducted on these vehicle configuration(s) at high altitude to calculate the fuel economy for the base level.

(b) For each model type, as determined by the Administrator, a city, highway, and combined fuel economy value will be calculated by using the projected sales and fuel economy values for each base level within the model type.

(1) If the Administrator determines that automobiles intended for sale in the State of California are likely to exhibit significant differences in fuel economy from those intended for sale in other states, he will calculate fuel economy values for each model type for vehicles intended for sale in California and for each model type for vehicles intended for sale in the rest of the states.

(2) The sales fraction for each base level is calculated by dividing the projected sales of the base level within the model type by the projected sales of the model type and rounding the quotient to the nearest 0.0001.

(3) The city fuel economy values of the model type (calculated to the nearest 0.0001 mpg) are determined by dividing one by a sum of terms, each of which corresponds to a base level and which is a fraction determined by dividing:

(i) The sales fraction of a base level, by

(ii) The city fuel economy value for the respective base level.

(4) The procedure specified in paragraph (b)(3) of this section is repeated in an analogous manner to determine the highway and combined fuel economy values for the model type.

7. A new § 600.209–85 is added to read as follows.

§ 600.209-85 Calculation of fuel economy values for labeling.

(a) For the purpose of calculating the EPA Fuel Economy Estimates for labeling, the manufacturer shall multiply the city model type fuel economy value determined in § 600.207(b), by 0.90, rounding the product to the nearest whole mpg, and

(b) Multiply the highway model type fuel economy value determined in § 600.207(b) by 0.78, rounding to the nearest whole mpg.

8. Section 600.306.85, is added to read as follows:

§ 600.306-85 Labeling requirements.

(a) Before offering a vehicle for sale, each manufacturer shall affix or cause to be affixed and each dealer shall maintain or cause to be maintained on each automobile:

(1) A general fuel economy label (initial, or updated as required in § 600.314) as described in § 600.307(b)(3) or;

(2) A specific label, as described in § 600.307(b)(4), for those automobiles manufactured or imported before the date that occurs 15 days after general labels are approved for the manufacturer.

(3) For any vehicle for which a specific label is requested which has a fuel economy value at or below the minimum tax-free value, the following statement must appear of the specific label:

[Manufacturer's name] may have to pay IRS a Gas Guzzler Tax on this vehicle because of its how fuel-economy unless the combination of mpg data from similar vehicles exceeds the minimum tax-free mpg.

(4)(i) At the time a general fuel economy value is determined for a model type, a manufacturer shall, except as provided in paragraph (a)(4)(ii) of this section, relabel, or cause to be relabeled, vehicles which:

(A) have not been delivered to the ultimate purchaser, and

(B) have a combined model type fuel economy value of 0.1 mpg or more below the lowest fuel economy value at which a Gas Guzzler Tax of $0 is to be assessed.

(ii) The manufacturer has the option of relabeling vehicles during the first five working days after the general label value is known.

(iii) For those vehicle model types which have been issued a specific label and are subsequently found to have tax liability, the manufacturer is responsible for the tax liability regardless of whether the vehicle has been sold or not whether the vehicle has been relabeled or not.

(b) The manufacturer shall include the current range of fuel economy of comparable automobiles (as described in §§ 600.311 and 600.314) in the label of each vehicle manufactured or imported more than 15 calendar days after the current range is made available by the Administrator.

(1) Automobiles manufactured before a date 16 or more calendar days after the initial label range is made available under § 600.311(c) may be labeled without a range of fuel economy of comparable automobiles. In place of the range of fuel economy of comparable automobiles, the label must contain a statement indicating that, as of the date of production or importation of this automobile, no range of fuel economy of comparable automobiles was available.

(2) Automobiles manufactured more than 15 calendar days after the initial or updated label range is made available under § 600.311 (c) or (d) will be labeled with the current range of fuel economy of comparable automobiles as approved for that label.

(c) The fuel economy label must be readily visible from the exterior of the automobile and remain affixed until the time the automobile is delivered to the ultimate consumer.

(1) The fuel economy label must be located on a side window. If the window is not large enough to contain both the Automobile Information Disclosure Act label and the fuel economy label, the manufacturer shall have the fuel economy label affixed on another window and as close as possible to the Automobile Information Disclosure Act label.

(2) The fuel economy label information may be included with the Automobile Information Disclosure Act label if the prominence and legibility of the fuel economy label is maintained. For this purpose, all fuel economy label information must be placed on a separate section in the lower or right hand portion of the label and may not be intermixed with the Automobile Information Disclosure Act label information except vehicle descriptions as noted in § 600.307(b)(5).

(3) The manufacturer shall have the fuel economy label affixed in a manner that appearance and legibility are maintained until after the vehicle is delivered to the ultimate consumer.

9. A new § 600.307-85 is added to read as follows:

§ 600.307-85 Fuel economy label format requirements.

(a) Fuel economy labels must be rectangular in shape, printed in a color which contrasts with the paper color and in a type size that is easily readable, and be large enough to allow inclusion of all required and voluntary information without distracting from readability.

(1) Within the height/width ratio range of 0.618 to 1.618, manufacturers may set their own label dimensions, as needed, keeping within the minimum requirements of:

(i) 95 millimeters (3.7 inches) high,

(ii) 100 millimeters (3.9 inches) wide, and

(iii) An area of 15,000 mm^2 (23.25 $inches^2$).

(2) At leat 60 percent of the total fuel economy label area, either the top or left portion, shall contain only the following information:

(i) The EPA logo in the upper left corner and Department of Energy logo in an adjacent corner.

(ii) The heading "Fuel Economy Estimates," highlighted by size or type face.

(iii) The city and highway fuel economy values, as described in paragraph (b)(1) of this section, of equal size and highlighting. The city value should be to the left or above the highway value.

(3) The fuel economy label shall have a contrasting border line at least 2.5 mm (0.1 inch) wide.

(b) Fuel economy labels, an example of which is illustrated in Appendix IX, shall contain in the format described in this section, at a minimum the following information:

(1) The city and highway fuel economy estimates, labeled accordingly, and calculated in accordance with § 600.209.

(2) The phrase "Compare this vehicle to others in the FREE Gas Mileage Guide, required by law at all dealerships." The word "FREE" shall be highlighted. The phrase shall be the first phrase in the label area not reserved for the fuel economy estimates, as described in paragraph (a)(2) of this section.

(3) The following vehicle descriptors will be used for general labels:

(i) Model year;

(ii) Vehicle car line;

(iii) Engine displacement, in cubic inches, cubic centimeters, or liters whichever is consistent with the customary description of that engine;

(iv) Number of engine cylinders or rotors;

(v) Engine description, if necessary to distinguish otherwise identical model type, as approved by the Administrator;

(vi) Fuel metering system, including number of carburetor barrels, if applicable;

(vii) Transmission class; and

(vii) Catalyst usage, if necessary to distinguish otherwise identical model types.

(viii) California emission control system usage, if applicable and if the Administrator determines that automobiles intended for sale in the State of California are likely to exhibit significant differences in fuel economy from those intended for sale in other states.

(4) The following vehicle descriptors will be used for specific labels:

(i) The descriptors of paragraph (b)(3) of this section;

(ii) Inertia weight class; and

(iii) Axle ratio.

(iv) Other engine or vehicle arameters, if approved by the Administrator.

(5) Where the fuel economy label is incorporated with the Motor Vehicle Information and Cost Savings Act label the vehicle descriptors, as set forth in paragraph (b) of this section, do not have to be repeated if the information is readily found on the Motor Vehicle Information and Cost Savings Act label.

(6) The phrase "Estimated annual fuel cost:" followed by the annual fuel cost. The annual fuel cost estimate for operating the automobile shall be computed by using values for the fuel cost per gallon, average annual mileage (both obtained through the Administrator from the Department of Energy), and the combined city/highway fuel economy determined in accordance with §600.209.

(i) The annual fuel cost estimate for a vehicle is computed by:

(A) Multiplying the estimated fuel cost per gallon for the model year, expressed in dollars to the nearest 0.05 dollar, by

(B) The average annual mileage, expressed in miles per year to the nearest 1,000 miles per year, and

(C) Dividing by the combined city/highway fuel economy value calculated using city and highway fuel economy value adjusted in accordance with § 600.209.

(ii) The product computed in paragraph (b)(6)(i) of this section and rounded to the nearest dollar per year will comprise the annual fuel cost estimate that appears on labels for that vehicle.

(7) The vehicle's classification (determined in accordance with § 600.315), the comparison range of city and highway fuel economy values for the class, and the date of the comparison range.

(i) The fuel economy range required by paragraph (b)(7) of this section is calculated and supplied to the manufacturer by the Administrator in accordance with § 600.311

(ii) If the Administrator has not supplied the fuel economy range for other vehicles to the manufacturer by the time a vehicle is to be labeled or within the time constraints of § 600.306(b), the statement required by paragraph (b)(7) of this section shall be replaced by the statement: "A range of MPG numbers for other models of similar size was not available when this vehicle was labeled."

(8)(i) For fuel economy labels of passenger automobile model types requiring a tax statement under § 600.513, the phrase "* * * Gas Guzzler Tax: $——— * * *" centered on a separate line within the fuel economy label. The words "Gas Guzzler" shall be highlighted.

(ii) The tax value required by this paragraph shall be based on the combined fuel economy value for the model type calculated in accordance with § 600.207 and rounded to the nearest 0.1 mpg. Adjustment in accordance with § 600.209 will not be used to determine the tax liability.

(c) The fuel economy estimates required by paragraph (b)(1) of this section shall be highlighted by being no less than six times the size of the next largest print on the label (excluding the title and logos) with each digit measuring at least 20 mm × 25 mm (0.75 inch × 1.0 inch) in width and height, respectively. The line width of each digit shall be at least 2.5 mm (0.1 inch). Digits not printed as a single large character shall be made of a matrix of smaller characters. The small characters shall not be separate alphabetic or numeric characters. The small characters shall form a reasonably dark and continuous line, to approximate a single large character.

§ 600.308–85 General labels. [Reserved]

10. Section 600.308–86 is added and reserved.

§ 600.309–85 Specific labels. [Reserved]

11. Section 600.309–85 is added and reserved.

12. A new § 600.311–85 is added to read as follows:

§ 600.311–85 Range of fuel economy for comparable automobiles.

(a) The Administrator will determine the range of city and the range of highway fuel economy values for each class of comparable automobiles.

(b) The range of city fuel economy values within a class is the maximum city and the minimum city fuel economy value for all general labels as determined in § 600.307(b)(3) regardless of manufacturer. The range of highway values is determined in the same manner.

(c) The initial range will be made available on a date specified by the Administrator that closely coincides to the date of the general model introduction for the industry.

(d) The ranges of comparable fuel economy values for a class of automobiles will be updated periodically and will be derived from the latest available label values reported to the Administrator for that class of automobiles.

(e) If the Administrator determines that automobiles intended for sale in California are likely to exhibit significant differences in fuel economy from those intended for sale in other states, he will compute separate ranges of fuel economy values for each class of automobiles for California and for the other states.

(f) For high altitude vehicles determined under § 600.310, both general and specific labels will contain the range of comparable fuel economy computed in this section.

(g) The manufacturer shall include the appropriate range of fuel economy determined by the Administrator in paragraph (c) or (d) of this section, on each label affixed to an automobile within that class except as provided in § 600.306(b)(7)(ii).

13. A new § 600.312–85 is added to read as follows:

§ 600.312–85 Labeling reporting and recordkeeping, Administrator reviews.

(a)(1) The manufacturer shall determine label values using the procedures specified in Subparts C and D of this part and submit the label values, and the data sufficient to calculate the label values, to the Administrator according to the timetable specified in § 600.313.

(2) The label values that the manufacturer calculates and submits under paragraph (a)(1) of this section shall constitute the EPA Fuel Economy Estimates unless the Administrator determines that they are not calculated accordingly to the procedures specified in Subparts C and D of this part.

(3) If at any time during the model year, any label values are determined not to be calculated according to the procedures specified in Subparts C and D of this part, the Administrator shall notify the manufacturer in writing. If the Administrator has sufficient information to enable calculation of the correct label values, this notification shall specify the correct label values which constitute the EPA Fuel Economy Estimates. If additional information is required, the Administrator shall request such additional information and a

recalculation of the label value by the manufacturer.

(4) If the Administrator determines revised label values under paragraph (a)(3) of this section are lower than the label values calculated by the manufacturer, the manufacturer shall affix the revised labels to all affected new vehicles which are unsold beginning no later than 15 calendar days after the date of notification by the Administrator.

(b)(1) The manufacturer is responsible for affixing vehicle labels that meet the format and content requirements of this subpart.

(2) The manufacturer shall retain for examination, at the Administrator's discretion, typical label formats representing all information required on the manufacturer's fuel economy labels. The information shall include the text of all required and voluntary information as well as the size and color of print and paper, spacing, and location of all printed information. Where the fuel economy label is incorporated with the automobile Information Disclosure Act label, the above requirements pertain to those sections of the label concerning fuel economy labeling information.

(3) If the Administrator determines upon examiniation of records that the label format or contents do not meet the requirements of this subpart, the Administrator may require the manufacturer to make specific changesx in subsequent labels. The Administrator may require such changes to be implemented on a reasonable timetable, but no sooner than 15 days from the date of notification to the manfacturer.

14. A new § 600.313–85 is added to read as follows:

§ 600.313–85 Timetable for data and information submittal and review.

(a) A manufacturer shall submit to the Administrator fuel economy label values and sufficient information to determine fuel economy label values within the following time constraints:

(1) For initial general label values, no later than five working days before the date that the model type is initially offered for sale.

(2) For the mid-year label update (as required under § 600.314(c)), the submissions for all model types must be made at least 5 working days before the implementation of new label values.

(3) For model types having label values updated because of running changes (as required under § 600.314(b)), the submission must be made at least five working days before the date of implementation of the running change.

(b) A manufacturer may not proceed with any label calculation until the data from each vehicle used in such calculation satisfies the requirements of § 600.008.

(c) If the Administrator has waived any testing in paragraph (b) of this section and subsequently finds that the decision to waive testing was based on an incorrect data submission or that a fuel economy offset exists (based on subsequent testing of that manufacturer's product line), the Administrator may require confirmation of the data generated by any such waived vehicle.

15. A new § 600.314–85 is added to read as follows:

§ 600.314–85 Updating label values, annual fuel cost, gas guzzler tax, and range of fuel economies for comparable automobiles.

(a) After the manufacturer calculates initial fuel economy values for a model type, those values will remain in effect for that model year unless updated in accordance with paragraph (b) or (c) of this section or unless revised in accordance with Section 312 of this part.

(b) *Continuous change label updates.* (1) Except as specified in paragraph (b)(2) of this section, the manufacturer shall recalculate the model type values for any running change under §§ 86.079–32, 86.079–33, or 86.082–34 that increases the equivalent test weight of any vehicle in the model type, adds an axle ratio which is 10 percent (or more) larger than the largest axle ratio tested in any base level, or increases the road-load horsepower for any vehicle in the model type by more than 10 percent since the most recent label value was determined using test data in accordance with § 600.507.

(2) For those model types created in § 600.207(a)(2), the manufacturer shall recalculate the model type values for any additons or deletions of sub-configurations to the model type. Minimum data requirements specified in § 600.010(C)(1)(ii) shall be met prior to recalculation.

(3) Recalculations shall be performed as specified in paragraph (d) of this section.

(i) The manufacturer shall use updated total model year projected sales for the recalculation in accordance with § 600.207 of this part.

(ii) All current model year data approved by the administrator for that model type shall be included in the recalculation

(c) *Mid-year label updates.* Each manufacturer shall recalculate label values once per year, in addition to any recalculations required under paragraph (b) of this section.

(1) All base levels used in the label calculations shall contain the minimum test data specified in § 600.010(c).

(2) The total model year projected sales shall be updated as of December 31 of the calendar year preceding the applicable model year.

(3) All current model year data approved by the Administrator as of December 31 shall be included in the recalculation.

(4) Recalculations shall be performed as specified in paragraph (d) of this section.

(5) The recalculated label values shall be used for labeling purposes no later than February 1 of the calendar year that is the same as the model year.

(d) *Recalculation Procedure.* (1) The difference between the fuel economy value currently used for labeling and recalculated values shall be determined as follows:

(i) The existing label values, calculated in accordance with § 600.207(b) (3) and (4), shall be rounded to the nearest 0.1 mpg.

(ii) The recalculated value, using the additional data cited in paragraph (b) or (c) of this section, shall be calculated in accordance with § 600.207. The values determined in accordance with § 600.207(b) (3) and (4) shall be rounded to the nearest 0.1 mpg.

(2)(i) If the city value calculated in paragraph (d)(1)(ii) of this section is less than the city value in paragraph (d)(1)(i) of this section by 1.0 mpg or more the manufacturer shall affix labels with the recalculated model type values (rounded to whole mpg's) to all new vehicles of that model type beginning:

(A) For label updates as described in paragraph (b) of this section, on the day of implementation of the running change.

(B) For mid-year label updates as described in paragraph (c) of this section, no later than February 1 of the calendar year that is the same as the model year.

(ii) If the highway value in paragraph (d)(1)(ii) of this section is less than the highway value in paragraph (d)(1)(i) of this section by 1.0 mpg or more the manufacturer shall affix labels with the recalculated model type values to all new vehicles of that model type beginning:

(A) For label updates as described in paragraph (b) of this section, on the day of implementation of the running change.

(B) For mid-year label updates as described in paragraph (c) of this section, no later than February 1 of the calendar year that is the same as the model years.

(3) If the recalculated city value is at least 1.0 mpg or more, or the recalculated highway value is at least 2.0 mpg more than the value currently used for the labeling, then the manufacturer has the option to use the new recalculated values for labeling the entire model type beginning on the day of implementation of the running change.

(e) For fuel economy labels using newly calculated fuel economy values in accordance with paragraphs (b) and (c) of this section, the manufacturer shall concurrently update all other label information (e.g., the annual fuel cost, range of comparable vehicles and the applicability of the Gas Guzzler Tax).

(f) The Administrator shall periodically update the range of fuel economies of comparable automobiles for all previously approved labels.

16. A new § 600.315–85, is added to read as follows:

§ 600.315–85 Classes of comparable automobiles.

(a) The Secretary will classify automobiles as passenger automobiles or light trucks (nonpassenger automobiles) in accordance with 49 CFR Part 523.

(1) The Administrator will classify passenger automoblies by car line into one of the following classes based on interior volume index or seating capacity except for those passenger automobiles which the Administrator determines are most appropriately classed as special purpose vehicles as provided in paragraph (a) (3) of this section:

(i) *Two Seaters.* A car line shall be classed as "Two Seaters" if the majority of the vehicles in that car line have no more than two designated seating positions as such term is defined in the regulations of the National Highway Traffic Safety Administration, Department of Transportation (DOT), 49 CFR 571.3.

(ii) *Minicompact cars.* Interior volume index less than 85 cubic feet.

(iii) *Subcompact cars.* Interior volume index greater than or equal to 85 cubic feet but less than 100 cubic feet.

(iv) *Compact cars.* Interior volume index greater than or equal to 100 cubic feet but less than 110 cubic feet.

(v) *Midsize cars.* Interior volume index greater than or equal to 110 cubic feet but less than 120 cubic feet.

(vi) *Large cars.* Interior volume index greater than or equal to 120 cubic feet.

(vii) *Small station wagons.* Station wagons with interior volume index less than 130 cubic feet.

(viii) *Midsize station wagons.* Station wagons with interior volume index greater than or equal to 130 cubic feet but less than 160 cubic feet.

(ix) *Large station wagons.* Station wagons with interior volume index greater than or equal to 160 cubic feet.

(2) The Administrator will classify nonpassenger automobiles into the following categories: Small pickup trucks, standard pickup trucks, vans, and special purpose vehicles. Pickup trucks will be separated by car line on the basis of gross vehicle weight rating (GVWR). For pickup truck car lines with more than one GVWR, the GVWR of the pickup truck car line is the arithmetic average of all distinct GVWR's less than or equal to 8,500 pounds available for that car line.

(i) *Small pickup trucks.* Pickup trucks with a GVWR less than 4,500 pounds.

(ii) *Standard pickup trucks.* Pickup trucks with a GVWR of 4,500 pounds up to and including 8,500 pounds.

(iii) *Vans.*

(3) All automobiles with GVWR less than or equal to 8,500 pounds which possess special features and which the Administrator determines are more appropriately classified as separate from typical automobiles or which do not meet the requirements of paragraphs (a) (1) and (2) of this section will be classified as *Special purpose vehicles.*

(4) Once a certain car line is classified by the Administrator, the classification will remain in effect for the model year.

(b) Interior volume index—passenger automobiles.

(1) The interior volume index shall be calculated, for each car line, in cubic feet rounded to the nearest 0.1 cubic foot. For car lines with more than one body style, the interior volume index for the car line is the arithmetic average of the interior volume indices of each body style in the car line.

(2) For all body styles, except station wagons and hatchbacks, with more than one seat (e.g., with a second or third seat) equipped with seatbelts as required by DOT safety regulations, interior volume index is the sum, rounded to the nearest whole 0.1 cubic foot, of the front seat volume, the rear seat volume, and the luggage capacity.

(3) For all station wagons and hatchbacks with more than one seat (e.g., with a second or third seat) equipped with seatbelts as required by DOT safety regulations, interior volume index is the sum, rounded to the nearest whole 0.1 cubic foot, of the front seat volume, the rear seat volume, and the cargo volume index.

(c) All interior and cargo dimensions are measured in millimeters (or inches) to the nearest whole millimeters (0.1 inch). All dimensions and volumes shall be determined from the base vehicles of each body style in each car line and do not include optional equipment. The dimensions H61, W3, W5, L34, H63, W4, W6, L51, H197, and volume V1 are to be determined in accordance with the procedures outlined in Motor Vehicle Dimensions SAE HS J1100a (Report of Human Factors Engineering Committee, Society of Automotive Engineers, approved September 1973 and last revised October 1979) except as noted herein:

(1) SAE HS J1100a(2.3) Cargo Dimensions—All dimensions measured with the front seat positioned the same as for the interior dimension measurement and the second seat (if applicable), for station wagons and hatchbacks, in the upright position. All head restraints shall be in the stowed position and considered part of the seat.

(2) SAE HS J1100a(5) Interior Dimensions. *L33-Maximum effective leg room-front passenger.* The dimension measured along a line from the ankle pivot center to the seating reference point (SgRP)—front (dimension "A" in the Appendix VIII figure) plus 254 millimeters (10.0 inches) with the front passenger's right foot placed on the depressed floor covering on the toeboard with the back of heel positioned at a line that bisects the angle formed by the extension of the normal toeboard and floor covering surfaces. Standard floor covering is to be used.

(3) SAE HS J1100a(7) Cargo Dimensions. *H198—Second seatback to load floor height.* The dimension measured vertically from the horizontal tangent to the top of the second seatback to the underpressed floor covering.

(4) SAE HS J1100a(8) Luggage Capacity—Total of volumes of individual pieces of a standard luggage set plus H-boxes stowed in the luggage compartment in accordance with the procedure described in 8.2. For passenger automobiles with no rear seat or with a rear seat with no rear seatbelts, the luggage compartment shall include the area to the rear of the front seat, with the rear seat (if applicable) folded, measured in accordance with paragraph (g)(2) of this section.

(d) The front seat volume is calculated in liters (cubic feet) by dividing 1,000,000 (or 1,728 as applicable) into the product of three terms following and rounding the quotient to the nearest 0.01 liter (0.001 cubic foot):

(1) H61—Effective head room—front (Obtained according to paragraph (c)).

(2)(i) (W3+W5+127)/2 for millimeters or (W3+W5+5)/2 for inches—Average of shoulder and hip

room—front, rounded to whole millimeters (0.1 inches) if hip room is more than 127 millimeters (5 inches) less than shoulder room (W3 and W5 are obtained according to paragraph (c) of this section), or

(ii) W3—Shoulder room—front, if hip room is not more than 127 millimeters (5 inches) less than shoulder room (W3 is obtained according to paragraph (c) of this section), and

(3) The arithmetic average of L34 (Maximum effective leg room—accelerator) and L33 (Maximum effective leg room-front passenger) rounded to whole millimeters (0.1 inches). L34 is obtained according to paragraph (c) of this section. L33 is calculated in accordance with Appendix VIII of this part.

(e) The rear seat volume is calculated in liters (cubic feet) for vehicles with a rear seat equipped with seat belts (as required by the Department of Transportation) by dividing 1,000.000 (or 1.728 as applicable) into the product of three terms listed below and rounding the quotient to the nearest 0.01 liter (0.001 cubic feet):

(1) H63—Effective head room—second. (Obtained according to paragraph (c) of this section.)

(2)(i) (W4+W6+127)/2 for millimeters or (W4+W6+5)/2 for inches—Average of shoulder and hip room—second, rounded to whole millimeters (0.1inches) if hip room is more than 127 millimeters (5 inches) less than shoulder room (W4 and W6 are obtained according to paragraph (c) of this section), or

(ii) W4—Shoulder room—second, if hip room is not more than 127 millimeters (5 inches) less than shoulder room (W4 is obtained according to paragraph (c) of this section), and

(3) L51—Minimum effective leg room—second. (Obtained according to paragraph (c) of this section.)

(f) The luggage capacity is V1, the usable luggage capacity obtained according to paragraph (c) of this section. For passenger automobiles with no rear seat or with a rear seat but no rear seatbelts, the area to the rear of the front seat shall be included in the determination of V1, usable luggage capacity, as outlined in paragraph (c) of this section.

(g) Cargo volume index:

(1) For station wagons, the cargo volume index V2 is the total of the volume of L Boxes (50 liter rectangular blocks measuring 250 x 400 x 500 millimeters) and M boxes (5 liter rectangular blocks measuring 125 x 160 x 250 millimeters) that can be placed in the cargo area in accordance with section 8.2 of HS J–1100a, substituting L and M boxes for the standard luggage set and H boxes, respectfully. The hidden cargo volume determined in accordance with paragraph (g)(3) of this section may also be included in the cargo volume index.

(i) The seat back of the rearmost seat equipped with seatbelts, as required by the Department of Transportation safety regulations, shall be in the upright position and the standard equipped spare tire, tools, or other vehicle parts normally stored in the cargo area shall be in their normal stored positions during the determination. The cargo area access door must close and lock freely without forcing or excessive slamming when all of the boxes used in the volume determination are in place.

(ii) The boxes shall be stacked from the rearmost seat as defined in paragraph (1)(i) of this section to the rear access door and from the cargo floor to the ceiling with soft point measurements (except for the cargo floor) used. No box shall protrude into the passenger compartment, that is, above the rearmost seat and forward of the vertical plane that is tangent to the back of the rearmost seat.

(iii) The M boxes used in the estimation of station wagon cargo volume shall equal no more than 20 percent of the total cargo volume of the vehicle.

(2) For hatchbacks, the luggage capacity procedure defined by the SAE for sedans will be used (SAE HS J–1100a(8)) except that the following additional conditions shall apply:

(i) A luggage piece may protrude above the height of the back of the rearmost seat, as defined in paragraph (1)(c) of this part, provided that the dimensional center of that piece is at least 50 mm (2 inches) below H197—front seat back to lower floor height or H198 second seat back to lower floor height, as applicable.

(ii) Hidden cargo volume determined in accordance with paragraph (g)(3) of this section may be included in the total cargo volume determination.

(iii) For hatchbacks with cargo covers:

(A) If the cargo cover is not removable or capable of storage, the cover is to be treated as part of the cargo compartment lid or access door and must close freely without forcing or excessive slamming with all of the luggage in place in the compartment.

(B) If the cover is removable or capable of storage, then cargo measurements may be made as in paragraph (g)(2)(i) of this section with the cover removed and placed within the cargo area or stored within the cargo area as designed by the manufacturer.

(3) Hidden cargo volume shall be determined by placing one or more M boxes into each hidden cargo area. A hidden cargo area is any space to the rear of the second seat that is distinct from the main open cargo area, designed by the manufacturer to accommodate small parcels, and which may have a door to separate it from the open cargo area. If a hidden cargo area is completely enclosed, the door must be capable of being closed and latched without forcing when all the M boxes used in the volume determination are in place.

(h) The following data for each body style in the car line covered by that label shall be made available to the Administrator upon request.

(1) For all passenger automobiles:

(i) Dimensions H61, W3, W5, L33, and L34 determined in accordance with paragraph (c) of this section.

(ii) Front seat volume determined in accordance with paragraph (d) of this section.

(iii) Dimensions H63, W4, W6, and L51 (if applicable) determined in accordance with paragagph (c) of this section.

(iv) Rear seat volume (if applicable) determined in accordance with paragraph (e) of this section.

(v) The interior volume index determined in accordance with paragraph (b) of this section for:

(A) Each body style, and

(B) The car line.

(vi) The class of the car line as determined in paragraph (a) of this section.

(2) For all passenger automobiles except station wagons and hatchbacks with one or more seats equipped with seatbelts as required by the Department of Transportation safety regulations:

(i) The quantity and letter designation of the pieces of the standard luggage set installed in the vehicle in the determination of usable luggage capacity V1, and

(ii) The usable luggage capacity V1, determined in accordance with paragraph (f) of this section.

(3) For station wagons with one or more seats equipped with seatbelts as required by the Department of Transportation safety regulations:

(i) The quantity and letter designation of the pieces of the set defined in paragraph (g)(1) of this section installed in the vehicle in the determination of cargo volume V2.

(ii) The cargo volume index V2 determined in accordance with paragraph (g)(1) of this section.

(4) For hatchbacks with one or more seats equipped with seatbelts as

required by the Department of Transportation safety regulations:

(i) The dimension H197 or H198, as applicable, determined in accordance with paragraph (c) of this section,

(ii) the quantity and letter designation of the pieces of the standard luggage set installed in the vehicle in the determination of usable luggage capacity V1,

(iii) The usable luggage capcity V1, detemined in accordance with paragraph (g)(2) of this section.

(5) For pickup trucks:

(i) All GVWR's of less than or equal to 8,500 pounds available in the car line.

(ii) The arithmetic average GVWR for the car line.

17. A new § 600.507–85 is added to read as follows:

§ 600.507–85 Running change data requirements.

(a) Except as specified in paragraph (d) of this section the manufacturer shall submit additional running change fuel economy data as specified in paragraph (b) of this section for any running change approved or implemented under §§ 86.079–32, 86.079–33, or 86.082–34 which:

(1) Creates a new base level or,

(2) Affects an existing base level by:

(i) Adding an axle ratio which is 10 percent (or more) larger than the largest axle ratio tested.

(ii) Increasing the road-load horsepower for a subconfiguration by 10 percent or more for the individual running change or when considered cumulatively since original certification (for each cumulative 10 percent increase using the originally certified road-load horsepower as a base).

(iii) Creating a new subconfiguration due to an increase in equivalent test weight within the configuration.

(b)(1) The additional running change fuel economy data requirement in paragraph (a) of this section will be determined based on the sales of the vehicle configurations in the created or affected base level(s) as updated at the time of running change approval.

(2) Within each newly created base level as specified in paragraph (a)(1) of this section, the manufacturer shall submit data from the highest projected total model year sales subconfiguration within the highest projected total model year sales configuration in the base level.

(3) Within each base level affected by a running change as specified in paragraph (a)(2) of this section, fuel economy data shall be submitted for the vehicle configuration created or affected by the running change which has the highest total model year sales. The test vehicle shall be of the subconfiguration created by the running change which has the highest projected total model year sales within the applicable vehicle configuration.

(c) The manufacturer shall submit the fuel economy data required by this section to the Administrator in accordance with § 600.313(a)(3).

(d) For those model types created under § 600.207(a)(2), the manufacturer shall submit data for each subconfiguration added by a running change.

§ 600.508–85 [Reserved]

18. Section 600.580–85 is added and reserved.

19. A new § 600.509–85, is added to read as follows:

§ 600.509–85 Voluntary submission of additional data.

(a) The manufacturer may, at his option, submit data in addition to the data required by the Administrator.

(1) Additional fuel economy data may be submitted by the manufacturer for any vehicle configuration which is to be tested as required in § 600.506 or § 600.507 or for which fuel economy data were previously submitted under paragraph (a)(2) of this section.

(2) Within a base level, additional fuel economy data may be submitted by manufacturer for any vehicle configuration which is not required to be tested by § 600.506 or § 600.507.

(b) The voluntary data submitted under paragraph (a)(2) of this section shall be submitted in rank order such that data is first submitted for all configurations with a higher sales fraction.

20. A new § 600.510–85 is added to read as follows:

§ 600.510–85 Calculation of average fuel economy.

(a) Average fuel economy will be calculated to the nearest 0.1 mpg for the classes of automobiles identified herein, and the results of such calculations will be reported to the Secretary of Transportation for use in determining compliance with the applicable fuel economy standards.

(1) An average fuel economy calculation will be made for the category of passenger automobiles that are domestically manufactured as defined in § 600.511(d)(1).

(2) An average fuel economy calculation will be made for the category of passenger automobiles that are not domestically manufactured as defined in § 600.511(d)(2).

(3) An average fuel economy calculation will be made for the category of light trucks which are defined in § 600.511(e)(1) and have two-wheel drive.

(4) An average fuel economy calculation will be made for the category of light trucks which are defined in § 600.511(e)(1) and have four-wheel drive.

(5) An average economy calculation will be made for the category of light trucks which are defined in § 600.511(e)(2) and have two-wheel drive.

(6) An average fuel economy calculation will be made for the category of light trucks which are defined in § 600.511(e)(2) and have four-wheel drive.

(b) For the purpose of calculating average fuel economy under paragraph (c), of this section:

(1) All fuel economy data submitted in accordance with § 600.006(e) or § 600.512(c) shall be used.

(2) The combined city/highway fuel economy will be calculated for each model type in accordance with § 600.207 of this section except that:

(i) Separate fuel economy values will be calculated for model types and base levels associated with car lines that are:

(A) Domestically produced, and

(B) Nondomestically produced and imported;

(ii) Total model year production data, as required by this subpart, will be used instead of sales projections;

(iii) The fuel economy value of diesel-powered model types will be multiplied by the factor 1.0 to convert gallons of diesel fuel to equivalent gallons of gasoline;

(iv) the fuel economy value will be rounded to the nearest 0.1 mpg;

(v) At the manufacturer's option, those vehicle configurations that are self-compensating to altitude changes may be separated by sales into high-altitude sales categories and low-altitude sales categories. These separate sales categories may then be treated (only for the purpose of this section) as separate configurations in accordance with the procedure of paragraph § 600.207(a)(4)(ii), and

(3) The fuel economy value for each vehicle configuration is the combined fuel economy calculated according to § 600.206 except that:

(i) Separate fuel economy values will be calculated for vehicle configurations associated with car lines that are:

(A) Domestically produced, and

(B) Nondomestically produced and imported;

(ii) Total model year production data, as required by this subpart will be used instead of sales projections; and

(iii) The fuel economy value of diesel-powered model types will be multiplied by the factor 1.0 to convert gallons of diesel fuel to equivalent gallons of gasoline;

(c) Except as permitted in paragraph (d) of this section, the average fuel economy will be calculated individually for each category identified in § 600.510(a), as follows:

(1) Divide the total production volume of that category of automobiles by

(2) A sum of terms, each of which corresponds to a model type within that category of automobiles and is a fraction determined by dividing

(i) The number of automobiles of that model type produced by the manufacturer in the model year by

(ii) The fuel economy calculated for that model type in accordance with paragraph (b)(2) of this section.

(d) The Administrator may approve an alternate calculation method if it is part of an approved credit plan under the provisions of Section 503(b) of 15 U.S.C. 2003(b).

21. A new §600.512–85 is added to read as follows:

§ 600.512–85 Model year report.

(a) For each model year, the manufacturer shall submit to the Administrator a report, known as the model year report, containing all information necessary for the calculation of the manufacturer's average fuel economy.

(b)(1) The model year report shall be in writing, signed by the authorized representative of the manufacturer and shall be submitted no later than 60 days after the report required in § 86.079–37 for the final production quarter.

(2) The Administrator may waive the requirement that the model year report be submitted within 60 days after the final quarterly production report. Based upon a request by the manufacturer, if the Administrator determines that 60 days is insufficient time for the manufacturer to provide all additional data required as determined in either §§ 600.506 or 600.507, the Administrator shall establish a date by which the model year report must be submitted.

(3) Separate reports shall be submitted for passenger automobiles and light trucks (as identified in § 600.510).

(c) The model year report must include the following information:

(1) All fuel economy data used in the labeling calculations and subsequently required by the Administrator in accordance with §§ 600.506 and 600.507.

(2) All fuel economy data for certification vehicles and for vehicles tested for running changes approved under §§ 86.079–32, 86.079–33, and 86–082.34.

(3) Any additional fuel economy data submitted by the manufacturer under § 600.509.

(4) A fuel economy value for each model type of the manufacturer's product line calculated according to § 600.510(b)(2).

(5) the manufacturer's average fuel economy value calculated according to § 600.510(c).

(6) A listing of both domestically and nondomestically produced car lines as determined in § 600.511 and the cost information upon which the determination was made.

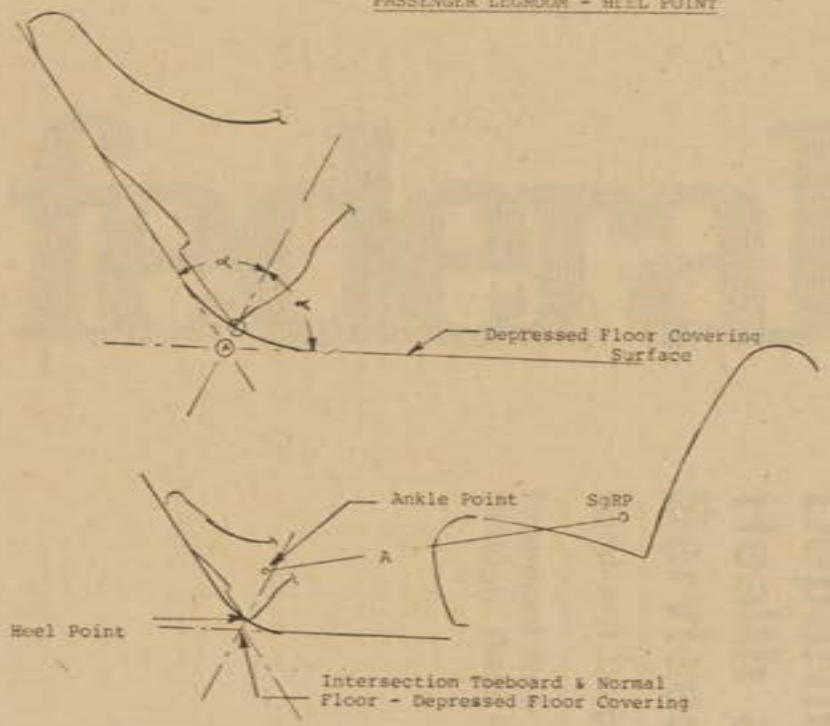
(7) Production data, the authenticity and accuracy of which shall be attested to by the corporation, and shall bear the signature of the chief executive officer.

22. Appendix VIII and IX are added as follows:

BILLING CODE 6560-50-M

FRONT PASSENGER LEGROOM DIMENSION TO BE USED IN DETERMINING VEHICLE INTERIOR VOLUME INDEX

PASSENGER LEGROOM - HEEL POINT



EPA Proposed Label Format

EPA

FUEL ECONOMY ESTIMATES

14 17

CITY ESTIMATE HIGHWAY ESTIMATE

Compare this vehicle to others in the FREE GAS MILEAGE GUIDE required by law at all new vehicle dealerships.
1982 BLUEBIRD 4.9 LITER, 8 CYLINDER, 2 VENTURI (MOVER) ENGINE, MANUAL 4-SPEED TRANSMISSION, AND 2.75 AXLE.
Estimated annual fuel cost: $1500.
The range of estimated fuel economy values of other MID-SIZE vehicles was from 12 to 42 mpg in the city and from 15 to 56 mpg in the highway as of September 18, 1981.

* * * GAS GUZZLER TAX: $1000. * * *

[FR Doc. 83-15183 Filed 6-8-83; 8:45 am]
BILLING CODE 6560-50-C

Federal Register

Thursday
June 9, 1983

Part III

Department of Health and Human Services

Food and Drug Administration

Proposed New Drug, Antibiotic, and Biologic Drug Product Regulations

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 312

[Docket No. 82N-0394]

Proposed New Drug, Antibiotic, and Biologic Drug Product Regulations

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to revise its regulations governing the review of investigational new drug applications and the monitoring of the progress of investigational drug use. FDA is taking this action to improve the investigational drug development process while maintaining high standards of human subject protection. The improvements are intended to assist sponsors of clinical investigations to prepare and submit high quality applications and to permit FDA to review them efficiently and with minimal delay. This action is one part of a larger effort to review and improve all aspects of FDA's drug regulatory process.

DATE: Comments by August 8, 1983.

ADDRESS: Written comments to the Docket Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Steven H. Unger, National Center for Drugs and Biologics (HFN-7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-5220.

SUPPLEMENTARY INFORMATION:

Introduction

This proposal is the second phase of efforts by the Department of Health and Human Services (HHS) and FDA to revise Federal regulations governing the new drug approval process. The first phase was a proposal published in the **Federal Register** of October 19, 1982 (47 FR 46622) to streamline the procedures in 21 CFR Part 314 for FDA review of new drug applications for marketing (NDA Rewrite). The second phase, contained in this document, addresses FDA's procedures in 21 CFR Part 312 for reviewing investigational new drug applications and for monitoring the progress of investigational drug use (IND Rewrite). Collectively, the IND/NDA Rewrite culminates an effort begun several years ago when FDA made concept papers available for public comment (44 FR 58919; October 12, 1979) and held a public meeting to discuss them (November 9, 1979).

The IND portion of the Rewrite reflects the continuing commitment of HHS Secretary Richard S. Schweiker and FDA Commissioner Arthur Hull Hayes, Jr., M.D., to facilitate the development, evaluation, and approval of safe and effective new therapies without compromising the underlying standards of safety and effectiveness upon which the American public has come to depend. Towards this end, the proposals reflect two major policy objectives. First, during the early phase of investigational research, FDA should focus on protecting the safety of human test subjects and give sponsors greater freedom to design, revise, and implement clinical research studies. This change should encourage innovation in drug development without compromising the safety of test subjects. Second, once the preliminary human studies have been completed and the drug appears to have marketing potential, FDA and drug sponsors should consult more closely to help ensure that the design of the major clinical trials are acceptable and will support marketing approval if the test results are favorable. Through better planning and closer consultation, FDA's later review of applications for marketing should proceed more efficiently. These changes will benefit the consumer by enhancing the prompt availability of safe and effective therapies.

Like the NDA portion of the Rewrite, the IND regulations have been reviewed by a special task force appointed by the Secretary, and chaired by the Commissioner, whose specific charge has been to review these regulations in accordance with Executive Order 12291 (46 FR 13193; February 19, 1981), the mandate of the President's Task Force on Regulatory Relief, and the policy objectives outlined above. Many of these issues were also previously reviewed by a separate FDA task force, which the Commissioner also chaired.

FDA's IND Rewrite proposal is designed to complement the October 19, 1982 NDA Rewrite proposal. That document proposed the following: a new streamlined format for marketing applications; the substitution of concise tabulations of essential clinical data in lieu of most case report forms; a new automatic appeals process for the prompt resolution of scientific disputes; a new policy on the acceptance of foreign data; more definite time frames for agency review; fewer supplements to approved applications along with fewer recordkeeping and reporting requirements; safety update reports while a marketing application is under review by the agency; and a strengthened adverse drug effect surveillance system after drugs have been approved for use by consumers.

These IND/NDA Rewrite proposals are part of a larger, overall effort to reform the drug development and review process. For example, FDA has instituted management changes aimed at enhancing accountability, improving utilization of personnel, and promoting timely communications with drug sponsors. The agency has also instituted some organizational changes, including the formation of the National Center for Drugs and Biologics, and the creation of a separate Office of Orphan Product Development within the Office of the Commissioner. Finally, as described in more detail below, FDA plans to issue guidelines on application format and on how to fulfill testing requirements. FDA believes that these initiatives, taken as a whole, should significantly improve the new drug approval process.

Highlights of this IND proposal, related issues, a description of the investigational new drug process, and the agency's economic analysis are summarized in the following introductory sections. The remainder of this preamble is devoted to a section-by-section analysis of the proposed regulatory changes.

Highlights of This Proposal

The major theme of the proposed IND regulations is that different stages of the IND process would be regulated differently. Safety concerns would predominate at the beginning of the process to ensure that research subjects are not exposed to unreasonable risk. In the later phases of drug investigation, FDA would also evaluate the scientific merit of study protocols to ensure that the planned clinical studies are capable of producing valid information on safety and effectiveness necessary to obtain marketing approval. This change in emphasis reflects the reality that only 20 percent of new chemical entities studied under an IND ever reach the NDA stage. Accordingly, FDA requirements and advice geared toward the development of a marketing application should wait until the drug has undergone the initial safety tests in human subjects and has shown some marketing potential. This proposal also clarifies the IND format, simplifies reporting requirements, and seeks to foster open, frank communications between FDA staff and drug sponsors. Finally, the regulations would give formal recognition to the idea of "treatment use" of certain drugs within the investigational context and

would also exempt certain studies on marketed drugs from most IND requirements (except Institutional Review Board review and informed consent). The specific changes are summarized as follows:

1. *Greater freedom during the early phase of human research.* The agency proposes to give drug sponsors greater freedom during the early phase of human research (Phase 1) by permitting such research to proceed unless it presents an unreasonable and significant risk to test subjects. FDA proposes to narrow the scope of its review of Phase 1 studies to focus on the safety of human test subjects. The proposal also articulates the flexibility available to clinical investigators in Phase 1 to modify protocols on the basis of experience gained during the investigation without prior notification to FDA, and further emphasizes to drug sponsors that the amount of toxicology and chemistry information required to be submitted in an IND depends on the nature and extent of the proposed clinical studies. As noted above, these changes to FDA's regulation of early research are intended to encourage innovation in drug development without compromising the safety of test subjects.

2. *Clearer format for IND submission.* The agency proposes to clarify the format for submission of an IND to create better organized applications and thereby facilitate agency review. This new format includes a greatly simplified cover sheet (Form FDA–1571), a brief overview of the investigational plan, and a brief introductory statement about the drug. The proposed format would also focus attention on the proposed human studies so that the supporting toxicology and chemistry information can be reviewed in light of the proposed clinical investigations.

3. *Clarified amendment procedures.* The agency proposes to clarify its amendment procedures by dividing amendments into several distinct categories: (i) Protocol amendments, for new protocols and changes in existing protocols; (ii) information amendments, for additional data as they develop; and (iii) IND safety reports. Each of these categories carries with it appropriate reporting intervals, depending upon the promptness needed for agency review. FDA also proposes to clarfify the scope of the annual reports to provide an overview of the progress to date and future plans for the IND, and to provide FDA with an update of the most significant safety information.

4. *Creation of explicit "clinical hold" procedures.* The agency proposes to codify procedures for instituting a "clinical hold," an order not to commence or continue a clinical study. For Phase 1 studies, FDA proposes to limit clinical holds to situations where there is an unreasonable and significant risk to human subjects. In later phases, the criteria would also include serious defects in study design that would render the study incapable of producing valid evidence of safety and effectiveness. To ensure uniform application of these criteria to similar drugs, all clinical holds would need to be approved by the director of the applicable reviewing division.

5. *Closer consultation between FDA and drug sponsors.* Although FDA has for several years offered "end-of-phase 2" conferences for drugs likely to provide significant and modest therapeutic advances, FDA now proposes to give the sponsor of any IND an opportunity to hold such a conference with the agency. The purpose of this meeting is to obtain concurrence on an overall plan for the conduct of Phase 3 trials and the design of specific studies. Such a "meeting of the minds" should significantly reduce the possibility of disputes later on after submission to FDA of a marketing application. FDA also proposes to place in its regulations the opportunity for a "pre-NDA" conference to discuss appropriate format and data presentation in a marketing application.

6. *Treatment use of investigational drugs.* The agency proposes to codify and state the conditions under which investigational drugs may be used to accomplish a treatment purpose in addition to an investigational purpose. This provision is designed primarily for drugs that have completed Phase 2 testing, when sufficient evidence of safety and effectiveness has already been obtained to justify making available an investigational drug for a treatment use. Such treatment uses would be limited to patients with serious diseases or conditions, for whom alternative therapies do not exist or cannot be used. Under these criteria, orphan drugs would be leading candidates for such treatment use. Accordingly, this provision implements a corresponding section of the recently enacted Orphan Drug Act, as described elsewhere in this preamble. FDA also proposes to simplify the procedures for obtaining investigational drugs for treatment use once these conditions are met.

7. *Exemptions for certain studies on marketed drugs.* Finally, FDA proposes to exempt from most IND requirements contained in Part 312 certain investigations conducted with drugs already approved for marketing for other uses. These would be limited to situations where safety is not an issue (because of a similarity in dose, route of administration, and patient population with the approved labeling) and where the investigations are not being conducted as a "pivotal study" for the purpose of changing the drug's labeling or advertising (e.g., adding a new indication or comparative safety claim). The exemption would apply primarily to researchers in academic or other institutions who are beginning to explore new uses for marketed drugs (i.e., not pivotal studies), or who are using the drug as a research tool. This provision is intended to reduce burdens on researchers and to permit FDA resources to be devoted to clinical investigations requiring FDA oversight and to review new drugs intended for marketing. Though exempt from most IND requirements in Part 312, such investigations would still be subject to other regulations designed to protect the rights and safety of patients, such as review by Institutional Review Boards (21 CFR Part 56) and informed consent (21 CFR Part 50), as these investigations are still subject to section 505 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355).

Related Issues

1. *Guidelines.* During the middle and late 1970's, the agency, with the help of its standing advisory committees, prepared over 25 guidelines devoted to the design of adequate and well-controlled clinical studies on different classes of drugs. These guidelines have facilitated high quality drug research and have been well received by drug sponsors. Therefore, FDA intends to expand the use of guidelines into other areas.

In the IND context, in addition to these clinical testing guidelines, the most pertinent guidelines are those related to animal toxicology testing and to chemistry and manufacturing controls requirements. As discussed elsewhere in this preamble, FDA intends to limit the scope of toxicology and chemistry submissions to that which is necessary to support the scope and duration of the proposed human testing. The guidelines are intended to help describe the scope of such submissions in the more common and expected circumstances. The new toxicology guidelines will update the current guidelines on this subject. The chemistry guidelines will be entirely new.

FDA recognizes that it is important, in issuing such guidelines, to solicit the views of experts throughout the scientific community, including government, industry, and academia.

Accordingly, FDA plans to hold public workshops about what should be in these guidelines to gain the views of members of the scientific community. The agency will publish the details of these workshops in future issues of the **Federal Register.**

FDA is also developing guidelines on appropriate formats for IND's. These guidelines should aid sponsors in organizing and presenting their submissions in a fashion most suitable for efficient agency review.

FDA believes that the planned revisions to existing guidelines and the creation of new guidelines should materially assist in the implementation of the new regulations. Thus, as noted above, the NDA Rewrite, IND Rewrite, and implementing guidelines are very much interrelated and should be viewed as a whole as increasing the efficiency of the new drug approval process.

2. *Outside review boards.* One option still under consideration by the agency, though not being proposed at this time, is the establishment of a "dual track" system whereby drug sponsors would have the option of submitting initial IND's either to FDA or to third party nongovernmental bodies. These outside groups would fall under the umbrella term of "Outside Review Boards" (ORB's). ORB's would parallel FDA in performing a "scientific review" of proposed human research studies, involving pharmacology, toxicology, chemistry, and clinical issues. The IND's being considered for this dual track system are the initial IND's that cover the first introduction of the drug into man and the early clinical pharmacolgy and effectiveness studies (Phase 1). Even under this dual track system, drug sponsors would still be required to submit their proposed human studies to local Institutional Review Boards (IRB's) for an "ethical review" and to ensure that research subjects give their informed consent.

The specifics of this outside review concept have varied over time. In the **Federal Register** of September 11, 1981 (46 FR 45538), FDA published a request for information, soliciting views as to whether local IRB's could assume the responsibility for reviewing certain IND's instead of FDA. Over 200 comments were received on that notice from hospitals, university medical centers, testing laboratories, IRB's, pharmaceutical manufacturers, academic and professional associations, and others. The concept of an IRB having sole responsibility for review of IND's was not favored by any category of comments. Most comments cited the lack of specialized scientific expertise of IRB's (especially regarding toxicology, chemistry, and pharmacology), the increased expense of expanding IRB's to gain the needed expertise, liability concerns, and the possibility that IRB's could take more time than FDA to review submissions. A number of comments, however, did suggest an optional system whereby a willing and expanded IRB could assume such review responsibility in lieu of an FDA review. Accordingly, FDA has redirected its consideration to this type of optional system which falls under the general umbrella term, ORB's.

Arguments in favor of ORB's are that FDA now tends to "overregulate" the early stages of human testing by delving into areas, such as study design, that should not concern FDA until later in the process when the drug has shown marketing potential. These arguments suggest that outside experts will be more prone to focus only on the central question of patient safety and leave these other matters to the discretion of the drug sponsor. ORB's are also perceived as a means of saving agency resources without compromising patient safety, as many drugs never advance beyond Phase 1 and so would never need to be seen by the agency.

Arguments against the dual track system start with the fact that FDA now reviews IND's promptly, and that in 90 percent of the cases the research may proceed within 30 days of the initial IND submission. Lengthy review times are therefore not often involved. Opponents also express concern about the possibility that "permissive" ORB's will surface, thereby letting drug sponsors "shop around" to find favorable reviewers, and that the "independence" of ORB's might be questioned where the drug sponsor provides large financial grants to the institution establishing the ORB. Finally, any FDA resource savings in IND review personnel may be more than offset by the additional resources necessary to develop standards for, inspect, and regulate ORB's.

FDA's preliminary view, apart from the possible advantages and disadvantages noted above, is that the dual track system may be unnecessary in light of the many other reforms contained in this proposal. As noted above, the agency itself is seeking to streamline the regulation of early research by narrowing the scope of Phase 1 review and by maximizing the flexibility with which drug sponsors may carry out early human investigations. By making these changes at FDA, the agency believes that the major goals of the dual track system can be achieved without the possible disadvantages noted above.

This issue, however, still remains under consideration by the agency. Therefore, FDA is soliciting comments as to whether, in light of the other changes being proposed in this document, the dual track system is worth pursuing, either on a permanent or pilot basis. In commenting on this issue, FDA requests responses to the following questions:

a. What specific benefits are attainable under a dual track system that are not attainable by making internal changes at FDA?

b. How can potential conflicts of interest be avoided? For example, should an individual drug sponsor be permitted to have its studies reviewed by an ORB whose institution receives financial assistance or grants from that drug sponsor?

c. What would be the appropriate degree of FDA oversight over ORB's, in terms of licensing, standard setting, and inspections?

d. Should FDA receive any concurrent notification (and, if so, in how much detail) or IND's submitted to ORB's for review?

e. If the dual track system were to be tried on a pilot basis, how long should the pilot program be tried, and how should the parameters of the pilot program be defined (e.g., by drug class and/or by authorizing a limited number of ORB's to operate)?

In addition, with respect to the possibility of a pilot program, FDA would like commenting institutions and drug sponsors to state whether they would be willing to participate in such an experiment.

FDA will carefully consider comments received on this proposal before reaching any final decision on whether to propose regulations involving Outside Review Boards.

3. *Bioresearch monitoring regulations.* The IND Rewrite proposal is intended to complement the agency's bioresearch monitoring regulations. Those regulations are the protection of human subjects in clinical investigations (21 CFR Part 50), the composition, operation, and responsibility of institutional review boards that review clinical investigations (21 CFR Part 56), and good laboratory practice for conducting non-clinical laboratory studies (21 CFR Part 58). In addition, the agency has also proposed regulations defining the obligations of clinical investigators (proposed 21 CFR Part 54; 43 FR 35210; August 8, 1978) and obligations of sponsors and monitors (proposed 21 CFR Part 52; 42 FR 49612; September 27, 1977).

The IND Rewrite proposal has been prepared on the assumption that clinical investigator and sponsor/monitor regulations will be made final before, or at the same time as, the IND Rewrite regulations. Accordingly, this proposal summarizes only the most essential clinical investigator and sponsor/monitor obligations and is completely silent on other issues (e.g., clinical investigator disqualification) that will be covered by the forthcoming bioresearch monitoring final regulations.

The Investigational New Drug Development Process

Almost all new drugs in the United States are developed by large pharmaceutical firms. These companies discover biologically active new molecules primarily by screening large numbers of synthetic compounds and natural products for various types of pharmacological activity. Those compounds that look promising are then subjected to short-term animal toxicity testing (1 week to 3 months, depending upon the anticipated duration of clinical testing) before being studied in humans. The preclinical testing is conducted to predict whether initial human studies will be acceptably safe and to predict, if possible, the drug's likely therapeutic activity. If the drug looks promising, human clinical studies are proposed in an investigational new drug application (IND).

Once an IND is filed with FDA, the sponsor must wait 30 days before testing the drug in humans. During this period, FDA reviews the submission to make sure the human subjects will not be subjected to unreasonable risks. If the agency is satisfied that the study does not pose such risks, the sponsor may begin testing the drug in humans. However, if FDA is concerned about the safety of the drug, or finds that more information is necessary to assess the safety issue, the agency notifies the drug sponsor not to begin human testing until the problems are resolved.

IND's are also reviewed by local IRB's for ethical acceptability. One goal of this review is to assure that human subjects are provided with sufficient information to be able to give their informed consent, a requirement that is statutorily mandated. IRB's are composed of scientific, medical, and lay personnel and are usually associated with the university, hospital, or clinic where the clinical research is to be undertaken. IRB's are regulated by FDA under regulations in Part 56.

Clinical investigations on new drugs are usually conducted by academic physicians working in university medical centers and by physicians in private practice. These investigations are frequently conducted on behalf of sponsoring drug firms, and the results may be published in the medical literature. Clinical testing proceeds progressively in three phases (called Phases 1, 2, and 3), each phase more extensive than its predecessor. (As noted below, the definitions of these phases are being revised in this proposal to reflect current practice.) As revised, these phases may be summarized as follows:

a. Phase 1 includes the initial introduction of the investigational new drug into humans. Phase 1 studies, which may be conducted in patients or normal volunteeer subjects, are designed to determine the metabolism and other pharmacologic actions of the drug, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. Phase 1 also includes research studies on drug metabolism, pharmacokinetics, structure-activity relationships, and mechanism of action in humans. Total Phase 1 exposure is quite small, generally in the range of 20 to 80 persons.

b. Phase 2 includes the early controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication in patients with the disease and to determine the common short-term side effects snd risks associated with the drug. Phase 2 trials are typically well controlled, closely monitored, and conducted in a relatively small number of patients (usually not more than several hundred).

c. Phase 3 studies are the expanded controlled and uncontrolled trials. They are performed after preliminary evidence of effectiveness of the drug has been established, and are intended to gather additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling. Phase 3 studies usually include from several hundred to several thousand patients.

Animal testing is also conducted during the human testing phases. As the human studies enlarge in scope and duration, further toxicology studies are needed to support them. Also, use of women of child bearing potential as test subjects must usually be preceded by reproductive performance and teratology studies in animals. Finally, once a drug appears to have marketing potential, long-term (chronic) animal studies, aproximately 1 to 2 years in duration, are usually conducted to predict possible latent human toxicities, including carcinongenicity.

FDA monitors the progress of an IND by reviewing IND amendments and annual reports submitted by the drug sponsor. Prompt reporting is required for significant safety findings, including certain adverse drug experiences in humans and important findings from animal toxicity studies. Such findings may result in the temporary suspension of a particular study or the termination of the entire IND if the safety subjects is placed in doubt. The agency also reviews new protocols submitted to the IND. In addition, when the sponsor so requests, agency officials assist in developing the overall clinical plan and designing specific protocols, most typically during an "End-of-Phase 2" conference with the drug sponsor, to ensure that planned studies are appropriate for the support of a marketing application.

Once the major IND studies are completed and the sponsor believes the data show the drug to be safe and effective under specified conditions, the sponsor submits to FDA an application to obtain the agency's approval for general marketing. Submission of a marketing application, however, usually does not mean that the IND file is closed. Some patients from earlier studies may still be receiving the investigational drug, or new clinical trials may have been commenced to study the drug for new indications. Accordingly, the IND remains active as long as patients are receiving the drug in an investigational context.

The process just described applies to a "commercial IND"—that is, an IND submitted by a pharmaceutical company or research center for the purpose of collecting safety and efficacy data necessary to gain marketing approval. In addition, FDA reviews "sponsor-investigator IND's" and "treatment IND's" which normally do not go through the entire three-phase IND process.

A "sponsor-investigator IND" is submitted by an individual researcher, often associated with an academic institution, in order to conduct exploratory therapeutic research or to use the drug as a research tool. A sponsor-investigator IND may involve either an unapproved drug or an approved drug for an unapproved use. If results from this research suggest marketing potential for the drug, further studies are usually conducted under the auspices of a commercial IND.

The term "treatment IND" applies to a request by a practicing physician to administer an unapproved drug primarily for treatment purposes within the investigational context. Such

treatment use may be appropriate for patients with serious disease conditions who are not responsive to approved therapies, such as in the case with orphan drugs. Ordinarily, a drug may be available for treatment use only after Phase 2 investigations have been completed.

In terms of overall number, FDA receives approximately 1,100 IND's for new drug and biological products each year. Of these, about 25 percent are commercial IND's, 30 percent are treatment IND's, and the remaining 45 percent are sponsor-investigator IND's. Accordingly, although most of the provisions in this proposal relate to commercial IND's, other provisions relate specifically to treatment IND's and certain sponsor-investigator IND's as well.

Economic Analysis

FDA has examined the economic consequences of the proposed changes in accordance with Executive Order 12291 and the Regulatory Flexibility Act (Pub. L. 96–354). The agency concludes that these revisions would have favorable economic impacts on the health care system, drug sponsors, and the agency without compromising the safety of human subjects. Although some of these favorable impacts are quantifiable, others with greater potential for savings can only be characterized in a very generalized, nonquantitative manner at this time.

Quantifiable impacts include an estimated net annual savings of $3.3 million to sponsors, arising from a simplified IND format; reduced and/or staged submission of manfacturing and controls data; a reduction in the number of amendments that are submitted during the first year that an IND is active; savings in start-up expenses associated with studies that would no longer be placed on clinical hold under the revised criteria; and savings of sponsor-investigator resources currently used to prepare IND's that will no longer be accepted. The only projected cost increase is modest by comparison and arises from requirements to improve the quality of annual reports. These revisions would also produce some savings in agency review resources.

A potential for substantially larger savings is presented by the provisions for increased use of guidelines, meetings, advice, and an appeals process to aid commercial IND sponsors in assembling the data for those IND's that lead to the submission of a marketing application. These initiatives, taken together, could result in substantial savings from fewer deficiencies being noted in the NDA review process due to better designed clinical trials, as well as further savings from the elimination of some unnecessary or poorly designed clinical studies.

The agency concludes that these revisions are not a major rule as defined in Executive Order 12291. The agency also certifies that the changes will not have a significant impact on a substantial number of small entities. The net savings, described above, will accrue to all sponsors, regardless of size, and the preponderance of unquantifiable savings will probably accrue to the public and to sponsors of commercial IND's, most of whom are not small entities. A copy of the agency's assessment of economic impact is on file with the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857.

The revisions to the IND regulations have a significance well beyond the specific cost reductions summarized above. As noted earlier, these regulations are part of a comprehensive review of the new drug approval process designed to accelerate the development and marketing of new drug therapies without compromising the safety and effectiveness of new drugs. Collectively, FDA's new regulations, guidelines, procedures, and policies should have considerable benefits. A quicker, more efficient drug development process means that the American public will have more safe and effective drugs sooner. A less costly drug development process means that the pharmaceutical industry will be able to develop more new drugs with the same number of research dollars, or alternatively to market less costly drugs. Either outcome will be of direct benefit to the American public. Most importantly, the prompt availability of safe and effective drug therapies has enormous potential benefit to patients and in public terms of improving the length and quality of life and in reducing health care and hospital costs. In addition, the provisions governing treatment use should be of special, if unquantifiable, benefit to patients with serious conditions who do not have adequate alternative therapies available to them, consistent with the goals of the recently enacted Orphan Drug Act.

Section-by-Section Analysis

FDA proposes to establish six new subparts in Part 312. Subpart A contains general provisions describing the scope of the regulations and the kinds of investigations that are exempt from IND requirements. It also describes the waiver provisions, labeling requirements, and requirements relating to the promotion and sale of investigational products. Subpart B describes the different kinds of applications and format, content, and reporting requirements for each of them. Subpart C contains regulations governing FDA review and action upon applications submitted under Subpart B, including clinical holds and terminations of IND's. Subpart D contains the general responsibilities of sponsors and clinical investigators during the course of a clinical investigation. Subpart E contains provisions on import and export of investigational drugs and a provision on the acceptability of foreign data in support of investigational and marketing applications. Finally, Subpart F describes requirements concerning the use of drugs in vitro and in animal testing.

Definitions. Under current regulations, "IND" stands for "Notice of Claimed Investigational Exemption for a New Drug." However, "IND" has come to be understood as standing simply for "investigational new drug application" and the proposed definition of "IND" would codify the simpler phrase.

As the IND regulations apply not only to "new drugs" but also to antibiotic drugs and biological products, "investigational new drugs" would be defined to include all members of these three categories of drugs that are either not approved for marketing or, if approved, are used in an investigational context outside of medical practice. Similarly, in identifying the submission needed to obtain approval to market a product, the proposal speaks in generic terms of a "marketing application" rather than specifically identifying the application appropriate to the drug (i.e., a new drug application (NDA) for new drugs, a request to provide for certification of an antibiotic (Form 5) for antibiotics, or a product license application for biological products.

The proposal would also define "clinical investigation" to mean any experiment in which an investigational new drug is administered or dispensed to, or used involving, one or more human subjects. In this context, an experiment is any drug use other than the use of a marketed drug in the practice of medicine.

The proposal would adopt definitions of "sponsor," "sponsor-investigator," "investigator," and "subject" that are like those used in the bioresearch monitoring regulations.

Finally, the proposal would revise the definitions of the phases of a clinical investigation to conform them to the current working understanding of the

distinctions between them. The regulations now consider both "Phase 1" and "Phase 2" to be parts of "clinical pharmacology," "Phase 1" involving studies in normal subjects, and "Phase 2" involving studies in patients. "Phase 3," under the current regulations, includes all clinical trials. The proposed revision would redefine Phase 1 to include clinical pharmacology testing both in normal subjects and in patients with the condition under investigation. What is currently "Phase 3" under the regulations would, under the revision, be divided into a new "Phase 2," representing the first small, rigidly controlled, clinical studies and a new "Phase 3," representing the expanded clinical trials. The proposed redefinitions in the regulations parallel current usage in the agency's clinical guidelines.

IND Format and Content

This section describes the format in which IND's should be submitted and the types of information IND's should contain.

Currently, IND format and content requirements are set forth in the IND Form FDA–1571, the application submitted by the sponsor to FDA. The form identifies in some detail the kinds of information a sponsor must submit in an IND. In general, such submission is required to include information on the drug's chemistry and manufacture, information about the pharmacology and toxicology of the drug derived mainly from animal studies, sufficient information about each clinical investigator to show that he or she is qualified to undertake the proposed investigations, information about any previous human experience with the drug, and protocols for each proposed study. The current form also performs several other functions, such as describing the sponsor's obligations with respect to the conduct of the investigation, describing some of the administrative actions FDA may take with respect to an IND, and defining the phases of an investigation.

FDA believes there are several deficiencies in the current content and format regulations that should be remedied. First, the statement of what is required to be submitted is needlessly complex and confusing and may lead some sponsors to submit more information than is actually required. Second, current applications are frequently submitted without the kinds of "abstracts" or introductory summaries that are of considerable help to the review process. Third, the current regulation fails to make clear that the technical information should be tailored to the nature and scope of the proposed clinical trials. Accordingly, the proposed revisions in IND format and content are intended to clarify IND submission requirements, to encourage the use of introductory and summary statements to facilitate administrative processing and review, and to emphasize that submission requirements vary with the phase and scope of the proposed clinical investigations.

More important than the actual structural changes, however, are the general principles set forth to guide sponsors in submitting IND's and FDA staff in reviewing them. FDA recognizes that many complaints with the IND system reflect not so much the regulations themselves as the superstructure that has grown up around them in practice. For example, although drugs and biologics have long been governed by the same IND regulations, drug IND's are usually at least twice as extensive as biologics IND's. Accordingly, the following principles are enunciated in the proposed regulations themselves in order to aid in the interpretation of the specific provisions.

The first such principle would be the FDA's primary objectives in reviewing an IND would be, in all phases of the investigation, to assure the safety and rights of subjects, and, in Phases 2 and 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety. Therefore, FDA's review of Phase 1 submissions would focus on assessing the safety of Phase 1 investigations. FDA's review of Phase 2 and Phase 3 submissions, however, would also include an assessment of the scientific quality of the clinical investigation and the likelihood that the investigations will yield data capable of meeting statutory standards for marketing approval. This principle is intended to reflect the agency's underlying policy goals to: (1) Encourage innovation by narrowing the scope of FDA regulation over early human research; and (2) increase the efficiency of the NDA review process through a heightened emphasis on advance FDA/sponsor consultation regarding the design of the major clinical trials.

The second basic principle is that the amount of information on a particular drug that must be submitted in an IND would depend upon the novelty of the drug, the extent to which it has been studied previously, the known or suspected risks, and the developmental phase of the drug and similar factors. This principle is intended to reflect the fact that flexibility in submission requirements is a function not only of the developmental phase of the research, but also of these other aspects of the drug itself.

The third principle is that the central focus of the first IND submission would be on the general investigational plan and the protocols for specific human studies. Subsequent amendments to the IND that contain new or revised protocols would build logically on previous submissions and would be supported by additional information including the results of animal toxicology studies or other human studies as appropriate. Annual reports to the IND would serve as the focus for reporting the status of studies being conducted under the IND and would update the general investigational plan for the coming year. This principle underscores the point that it is the scope and nature of proposed protocols that are of central importance in determining how much information needs to be submitted and in focusing on the degree of safety that needs to be shown.

The new IND format itself would consist of a cover sheet (revised Form FDA–1571), a table of contents, some introductory material intended to provide an overview of the investigation, the protocols for each study, and the technical information to support those specific protocols. This format may be further described, as follows:

1. *Cover sheet (Form FDA–1571).* FDA proposes to transform the IND Form FDA–1571 from a repository of the regulations to simply a cover sheet for the IND. The new Form FDA–1571 would only identify the phase or phases to be conducted and would contain essential "identifier" information about the sponsor and monitor of the investigation. When signed by the sponsor or the sponsor's representative, the application would commit the sponsor to comply with all applicable provisions governing the investigational use of drugs, as described in Part 312 as well as Parts 50, 52, 54, and 56. If the sponsor does not reside in the United States, the sponsor would designate an agent who resides or maintains a place of business in the United States who would also sign the form. This provision regarding foreign sponsors would correspond to a similar provision in the NDA Rewrite proposal.

2. *Introductory sections.* The proposed IND format would begin with a table of contents and a brief introductory statement. The introductory statement, which the agency believes should not usually be more than two or three pages in length, would give a broad overview

of the proposed investigation. It would give the drug's name, its pharmacological class, a short statement of the objectives of the proposed study, and a brief summary of previous human experience with the drug, including any foreign experience. FDA believes that the statement would be of considerable benefit in facilitating review by helping assign IND's to the appropriate reviewing division in an expeditious manner and by quickly orienting reviewers to the contents of the IND. Following the introductory statement, the IND would contain a general plan for the proposed investigation. This document would give a "blueprint" for drug development—that is, the kind and number of studies to be conducted in the following year, the general approach to be followed, and an estimate of the number of subjects to be involved. This "blueprint" is one mechanism for focusing attention on the scope and extent of the proposed human studies, both for sponsor submission and FDA review purposes.

3. *Protocols.* The general investigation plan would be followed by a protocol for each study the sponsor intends to begin at the end of FDA's 30-day review period. Protocols for later studies may be submitted in the initial IND or in protocol amendments as the investigation progresses. The detail of Phase I protocols now submitted by drug sponsors provides one of the best examples of where current practice has superseded the actual letter of the regulations. Although the current regulations require only a "general outline" of Phase 1 studies, in practice most Phase 1 studies have been submitted in the kind of detail more appropriate for Phase 2 or 3 protocols. Accordingly, in drafting revised regulations, FDA has sought to emphasize the difference in requirements between Phase 1 protocols and protocols for Phases 2 and 3.

Although the proposal would require protocols for all phases to contain information on subject selection criteria, on investigator qualification, on proposed procedures for monitoring the clinical effects of the drug, and so on, the proposal would stress that the amount of detail needed on each aspect of the protocol would vary with the phase of the investigation. The revision would reflect FDA's focus in Phase 1 on safety issues and would make clear that FDA expects Phase 1 protocols to be submitted in an outline form that would need to contain sufficient detail to permit a reliable assessment of subject safety, but not more than necessary for an adequate review.

The revision would also stress the flexibility a sponsor has to modify a Phase 1 protocol as experience dictates without having to submit protocol amendments to FDA (provided such modification is described in the next annual report). This flexibility reflects the truly experimental nature of early research and is consistent with the broad policy objective of maximizing sponsor freedom during this stage. Although this flexibility is available under current requirements, it has not been fully appreciated in practice by FDA or investigators and sponsors.

As noted above, FDA's review of Phase 2 and Phase 3 submissions has a broader scope. At this stage FDA is concerned not only with subject safety, but also with an assessment of the scientific quality of studies and the likelihood that the studies will produce the kind of data that can be considered in determining whether to approve a drug for marketing. Therefore, to decrease the chance that such studies will not meet statutory standards for marketing approval, much more detailed information about study design is required for Phase 2 and 3 investigations. FDA has prepared over 25 clinical guidelines for different classes of drugs that describe appropriate ways of designing and conducting these Phase 2 and Phase 3 trials.

One additional minor change should be mentioned. Under current regulations, protocols for early phase studies must identify "any expert committees or panels to be utilized," although protocols for later phases need not. The justification for this difference is no longer evident, and the IND Rewrite would require that each protocol, regardless of phase, identify the name and address of its reviewing institutional review board (IRB). This minor change will provide FDA with immediate access to the identity of a particular IRB, if necessary.

4. *Chemistry, manufacturing, and control information.* This section states the requirements regarding the submission in the application of information about the composition of the drug substance and drug product, their specifications, and their methods of manufacture and control. The section would clarify rather than substantially revise current requirements. FDA is preparing guidelines on the scope and content of chemistry, manufacturing, and control submissions. The language of the proposed regulation is intended to be general in nature so that it may accommodate changes that might be made as a result of the guideline development process.

The proposed revision emphasizes that chemistry, manufacturing, and control information should be tailored to the scope and duration of the proposed clinical investigation. For example, if relatively short-term clinical tests are planned, the stability information required would be limited to that needed to demonstrate that the product would be stable for the short duration of the investigation.

The revision would continue to require the submission of sufficient information about the drug substance and drug product to ensure its identity, potency, quality, and purity and to ensure that there is a sufficient continuity in the product so that information obtained from previous clinical and nonclinical studies can be considered in assessing the safety of future studies. It would also require a description of the method of preparation (or isolation) of the drug substance and a brief general description of the manufacturing and packaging of the drug product.

5. *Pharmacology and toxicology information.* FDA also does not propose to change significantly the substance of the current requirements regarding submission of animal and in vitro test results. The results of such tests serve primarily to support FDA's assessment of the safety of proposed clinical investigations. These studies are directed toward defining the drug's safety, toxicity, and pharmacological action rather than its efficacy. They are meant to predict effects which might be expected when the drug is administered to human subjects.

The proposal would retain the current requirement for "adequate information" on the basis of which the sponsor has concluded that it is reasonably safe to begin the proposed study. The proposal, like the current regulation, would note that the kind, duration, and scope of such tests would depend on the nature of the proposed investigations. The proposal would identify only in a general way the kinds of tests that sponsors would ordinarily submit in an IND. Detailed information on what kinds of tests may be submitted to support specific kinds of clinical investigations is contained in toxicology guidelines. The agency is reviewing its toxicology guidelines, and, as noted earlier, plans to develop new guidelines with the help of scientific experts from both inside and outside of government.

The proposal would also specify an appropriate format for toxicology submissions. The sponsor would be

required to submit an integrated summary of the toxicological effects of the drug in animals and in vitro and, for each study submitted primarily to support the safety of a proposed investigation, a full tabulation of the data. The latter provision reflects the fact that, unlike most other technical data, the usefulness of much toxicology data is largely confined to the investigational stages of drug development. Because such data's utility is greatest at this early stage, it is appropriate that it be submitted in the kind of detail appropriate for careful scrutiny.

6. *Sponsor-investigator IND's.* It should be emphasized that the proposed application section describes the information a commercial sponsor must submit for a previously unstudied new molecular entity. In general, it does not describe the kinds of technical information needed to support a sponsor-investigator research study of a previously studied drug product. FDA expects that in most such cases technical information previously submitted to FDA by the commercial sponsor will be incorporated by reference into the sponsor-investigator's IND, assuming permission is granted by the commercial sponsor. FDA will make available guidelines to assist sponsor-investigators in preparing IND's.

Amendments to the IND

This section describes the types and timing of IND amendments that must be submitted during the time that a drug is under investigational status. These amendments fall into three categories: (1) Protocol amendments, (2) information amendments, and (3) adverse drug experience reports. The proposed revisions are intended to rationalize the flow of information to an active IND file, to clarify when amendments are required, and to establish formatting requirements that will simplify their processing and review.

1. *Protocol amendments.* Current regulations require that a sponsor conducting an investigation adhere to the protocols described in the IND submission. If the sponsor intends to expand the scope of the investigation or to alter its direction, the sponsor is required to amend the IND to reflect the change. The current regulations, however, do not specify when an amendment should be submitted, for what kinds of changes amendments are required, or what the amendment should contain. The lack of specificity in the regulations means all too frequently that amendments are submitted in such a fashion that it is extremely difficult for reviewers to gain an understanding of their significance or their relationship to previous or subsequent submissions, except by reviewing the complete IND file. This difficulty in tracking an IND once an investigation begins may explain in part current emphasis on the initial IND submission.

The proposal would make clear that FDA is interested only in learning contemporaneously about the kinds of changes that bear directly on its review and monitoring responsibilities. Thus, under the protocol amendment procedures, amendments would be required only for new protocols, for protocol changes that significantly relate to the agency's assessment of an investigation's safety, and, for Phase 2 and Phase 3 studies, also for protocol changes that significantly relate to the scope of an investigation or to its scientific quality. Additionally, a protocol amendment would be required to list a new investigator that is added to an already submitted protocol. FDA reviews each new investigator to ensure that the investigator is qualified to conduct the proposed research and to verify that the investigator is eligible to receive investigational new drugs.

The proposal would also clarify the proper timing of submissions. The current IND regulations require the sponsor to notify FDA before beginning a substantially modified protocol or a new protocol, but do not require sponsors to pause before proceeding, so long as local IRB approval has been obtained. The IND Rewrite would explicitly retain this current process. The only change being made here is that protocol amendments which merely list a new investigator to an already submitted protocol would be sent to FDA under the timetable described below for information amendments.

Finally, FDA proposes to create a standard format for protocol amendments that would make them much easier to process and review. The flow of protocol amendments to the IND under current requirements is such that it is frequently difficult to determine the contents of an amendment, the sequence of amendments, or even to determine what specific protocol in an IND a submission is intended to amend. To remedy these deficiencies, the proposed revision would require that all protocol amendments be prominently identified, that they be numbered iin sequence of submission, and that protocol changes plainly indicate what specific protocols they are amending. The proposal would also require that a protocol amendment cite any specific technical data that support the proposed new protocol or protocol change. If, for example, the sponsor proposed to undertake a new long-term trial of 6 months' duration, where all previous trials had not exceeded 1 month, the sponsor would be required to cite the specific animal studies that supported a trial of this length. Such supporting data would either have been previously submitted to the IND or would be concurrently submitted in an information amendment.

2. *Information amendments.* The current regulation provides that the IND may be "amended or supplemented from time to time on the basis of experience gained with the * * * drug." The regulation contains no other guidance on the submission of additional technical information after the initial IND is submitted. The IND Rewrite would add specificity by establishing an "information amendment" as a means for conveying to FDA information on significant changes in the technical content of the IND file. Information amendments would provide specific technical information, including chemistry, toxicology, and pharmacokinetic data. Information amendments would serve primarily two functions: (i) They would provide the technical support (usually essential toxicological or chemistry information) for new or modified clinical protocols; and (ii) they would be a mechanism for keeping current the information contained in the IND file. The format of information amendments would be similar to that of protocol amendments.

Thus, information amendments would be required to bear prominent identification of their contents and to be serially numbered by discipline. Additionally, to facilitate FDA review, information amendments would be required to contain a statement of the nature and purpose of the amendment and to be submitted in a fashion appropriate for scientific review.

The proposal would also establish a new system for timing of information amendment submissions. Currently, the frequency and number of separate amendments and other communications submitted to an IND file places a significant workload on the agency. This results in delaying the routing of documents to the reviewing divisions. The proposal therefore encourages sponsors to group together information amendments and to submit them together at 30-day intervals instead of submitting these amendments individually. The grouping of amendments should ease both the agency's administrative burdens and the organizational and shipping burdens placed on sponsors. Of course, the

agency recognizes that in some cases the progress of an investigation may not permit the grouping of amendments, such as when information amendments are needed to support a protocol amendment that must be submitted more promptly. However, even when submissions are needed more often than every 30 days (so as not to impede the progress of the investigation), FDA encourages sponsors to group submissions as much as possible in order to improve the functioning of FDA document control.

To alleviate the administrative difficulties described above, FDA requests sponsors to group amendments at 30-day intervals (or earlier, if necessary) on an interim basis, pending completion of the notice and comment rulemaking proceeding. FDA believes such implementation is permissible prior to publication of a final rule because the change only affects the timing, not the content, of the submissions.

3. *IND safety reports.* The IND Rewrite contains a separate section on safety reports to highlight the importance of monitoring patient safety throughout the IND process. The proposal retains the current requirement for sponsors to notify FDA and all participating investigators about any information the sponsors receive associated with the use of the drug that may suggest significant hazards, contraindications, side effects, or precautions; the proposal states that, in meeting this requirement, the sponsor is required to review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from any source, foreign or domestic, including information derived from clinical investigations, animal investigations, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers. (Under the proposed rule defining the obligations of clinical investigators, an investigator is responsible for relaying to the reviewing IRB information received from the sponsor about adverse effects.) The proposal defines "information relevant to the safety of the drug" to include information about related drugs. The proposal also defines "associated with the use of the drug" to mean there is a reasonable possibility that the event may have been caused by the drug. To meet this definition, the causal relationship between the drug and the adverse event need not be known with any degree of certainty and, when doubt exists, the regulation should be construed to require submission of an IND safety report.

In addition, the proposal specifies time frames within which a sponsor would be required to relay safety reports to FDA. The current requirement is that an "alarming" finding must be reported "immediately" and that all other findings must be reported "promptly." Under the proposal, a sponsor would be required to notify FDA about fatal or life-threatening clinical experiences not previously reported as soon as practical and in no event later than 3 working days after the sponsor initially receives the information. Other serious adverse events would be required to be relayed to FDA as soon as possible and in no event later than 10 working days after the sponsor initially receives the information.

To ensure that this information is rapidly transmitted to FDA, the proposal would require the sponsor to relay the 3-day and 10-day IND safety reports by telephone at the same time as Written notifications are submitted. Telephone calls are to be made to the FDA division with review responsibility for the IND. written notifications are to be prominently identified to facilitate expedited processing by the agency.

The proposal would also retain the requirement obliging sponsors to investigate thoroughly all safety related information received by them. Although FDA understands that these investigations will not ordinarily be completed within the time limits prescribed for the IND safety reports, the proposal would require sponsors to submit relevant followup information to the 3-day and 10-day reports as expeditiously as practicable in an information amendment. Followup information on incidents not triggering a 3-day or 10-day report would be submitted, as appropriate, in either an information amendment or an annual report.

Annual Reports

This section describes content requirements for annual reports. Current regulations require a sponsor to submit accurate progress reports of the investigation and significant findings together with any significant changes in the investigator brochure at reasonable intervals, not exceeding once a year. FDA has found such reports to be a valuable means of monitoring the progress of investigations and therefore proposes to retain the provision in the rewrite. However, because current regulations provide inadequate guidance on what should be included in a progress report, the quality of such reports has varied considerably. Annual reports have varied from a very brief and conclusory statement about a sponsor's activities to a comprehensive statistical analysis of all data collected. Accordingly, some sponsors submit too much information and others submit too little.

The revision would clarify what FDA regards as the minimum amount of information needed to monitor satisfactorily the progress of drug development. It would require a brief summary of the status of each clinical study in progress, a brief summary of safety information obtained in the previous year, and a description of the general investigational plan for the following year. As part of the summary of safety information from the previous year, the annual report would contain a listing of patients who died or dropped out of clinical studies, because these patients are likely to provide the most important safety information. (The annual update of safety information would necessarily summarize all IND safety reports submitted to FDA throughout the previous year.) This requirement is consistent with a provision in the NDA Rewrite proposal that would require the routine submission of case report forms for those patients meeting these same criteria (i.e., persons who died or dropped out). Finally, as an aid in fostering better communication between FDA and the sponsor, the sponsor could use the annual report to identify any outstanding business about which the sponsor would like to meet with FDA or to have a written reply or comment from the agency.

Use of Investigational Drugs for Treatment

This section codifies a special procedure authorizing the "treatment use" of investigational drugs in an investigational context.

When reports in the medical literature begin to appear that a new investigational drug shows promise for a serious disease, a demand for the drug for the benefit of patients frequently develops. FDA has responded to this demand by permitting physicians to obtain investigational drugs for treatment use either under physician sponsored IND's or under protocols that are part of commercially sponsored IND's. In addition to providing patients with needed drug therapy, such treatment uses are a valuable adjunct to the investigation as well, frequently providing sponsors and FDA with valuable safety data. Although the agency has for many years permitted selected investigational drugs to be distributed primarily for treatment use

under these circumstances, the current IND regulations do not specifically authorize the practice. The proposed revisions would expressly authorize this use of investigational drugs, define the universe of drugs eligible for treatment use, and describe the procedures by which these drugs can be obtained.

Under this proposal, a drug would be obtainable for treatment use either under a treatment protocol submitted by the sponsor of an active commercial IND for that drug or under a separate treatment IND submitted by a licensed medical practitioner. The proposal would make plain that the primary purpose of a treatment protocol or treatment IND is to provide patients with a drug to treat a serious disease condition not treatable satisfactorily with alternative therapies. The criteria for authorizing the use of an investigational drug for treatment would reflect this purpose. Thus, FDA would only authorize use of a drug under a treatment protocol/IND if it found: (1) That the proposed use is intended for a serious disease condition in patients for whom no satisfactory approved drug or other therapy is available; (2) that the potential benefits of the drug's use outweigh the potential risks; and (3) that there is sufficient evidence of the drug's safety and effectiveness to justify its intended treatment use. These criteria would ordinarily mean that a drug would not be a candidate for a treatment use until it had gone through the kind of studies conducted during Phase 2. Thus, investigational drugs would ordinarily only become available for a treatment use at the end of Phase 2 or during Phase 3 of an investigation.

FDA believes that there are several reasons for generally confining the availability of investigational drugs for treatment use to drugs in this time frame. First, the kind of evidence necessary for FDA to be able to make an adequate assessment of the drug's potential benefits is usually not available until this time frame. Second, the agency wants to ensure that the treatment protocol/IND system does not undermine patients' interest in participating in controlled clinical trials. If access to investigational drugs for "treatment" becomes too widespread too early in the process, this could impede the collection of the type of data necessary to obtain marketing approval. Accordingly, FDA believes that the model for treatment protocol/IND use should be a drug in Phase 3 when the major clinical trials are completed or underway and where the evidence to date is favorable toward subsequent approval for marketing. The "Group C" system at the National Cancer Institute has followed these same principles and has achieved considerable success.

FDA anticipates that the proposed criteria for making a drug available under a treatment IND/protocol will be adequate to meet the vast majority of treatment use requests. Where compelling circumstances warrant, however, FDA will consider permitting treatment use earlier in the IND process.

Under the proposed criteria, "orphan drugs" would be leading candidates for treatment use by virtue of their being intended for rare diseases without satisfactory alternative therapy. As stated in the Orphan Drug Act (Pub. L. 97–414; January 4, 1983), sponsors of IND's for orphan drugs should be encouraged to design clinical studies that permit the inclusion of patients who wish to receive the drug for treatment purposes. (See section of Pub. L. 97–414 entitled, "Open Protocols for Investigations of Drugs for Rare Diseases or Conditions.") Accordingly, the treatment use section of the proposed regulations serve to implement the corresponding provisions of the Orphan Drug Act.

FDA has been criticized for not adequately informing the medical commuity about the availability of certain investigational drugs for treatment use. The proposal is intended to improve physician (and patient) access to these investigational drugs in three ways. First, by placing the procedures in the regulations, the necessary steps for obtaining such drugs will be made clear and more generally known. Second, as described below, FDA is encouraging commercial sponsors to develop treatment protocols so that, in most instances, the individual physician should not even have to come to FDA. Third, when separate treatment IND's do need to be submitted to the agency, the necessary paperwork is minimal, designed primarily to ensure patient safety, and the type of information needed to be submitted should be readily accessible to the treating physician. Accordingly, this provision should provide considerable benefits to consumers.

For some of the most promising investigational drugs, requests for the drug for treatment of individual patients can extend into the hundreds. The regulation would encourage drug companies to accommodate such requests under company-developed treatment protocols rather than to act simply as a supplier to many individual physicians, each of whom would otherwise have to submit a separate treatment IND. A company-sponsored treatment protocol has several advantages. Such a protocol can be readily designed to collect important, useful, and easily interpreted data about the drug, especially regarding safety.

It would certainly be in the public interest to utilize that additional premarketing data base. In addition, by channeling a number of physicians' requests for a drug for treatment into a single treatment protocol, scarce agency resources may be saved which can then be devoted to other IND's and marketing applications. In this regard, it should be noted that treatment IND's submitted by individual physicians now account for approximately 30 percent of all IND's received by FDA in a typical year.

Whether the request for use of an investigational drug in treatment were to be submitted in a treatment protocol or in a treatment IND, FDA' requirements would be minimal, consistent with patient safety and proper use. The protocol for each would include an explanation of the rationale for use of the drug, a brief description of the criteria for patient selection, a description of the clinical procedures, laboratory tests, or other measures to be taken to monitor the effects of the drug and to minimize risk, and a description of the proposed dosage and administration. Such protocols might be written by either the drug firm supplying the drug or an individual physician sponsor, with input from FDA as necessary to aid patient safety and proper use.

Because toxicology, chemistry, and other technical information should already be available for FDA review in the commercial sponsor's IND, in general little or no additional supporting information would be required for either a treatment protocol or a treatment IND. In the case of a treatment IND submitted by a individual physician, however, the physician needs permission from the commercial sponsor for FDA to cross-reference such technical information from the commercial sponsor's IND into the physician's treatment IND. In the normal course, if a commercial sponsor chooses to provide the individual physician with the investigational drug, FDA would view that shipment of the drug as authorization by the commercial sponsor to permit FDA to incorporate by reference the technical information in the commercial sponsor's IND into the physician's treatment IND. Such incorporation by reference makes the information available to FDA for review purposes, but does not authorize disclosure to the physician of the information so incorporated.

The obligations of sponsors and investigators on the conduct of investigational uses under treatment protocols/IND's would in general be identical to those imposed on other sponsors and investigators. Thus, the requirements regarding the control of the drug, recordkeeping, and reporting of safety information would apply in the treatment protocol/IND context as well. Although investigators are normally obliged under the IRB regulations in Part 56 to obtain the review and approval of a local IRB, FDA would carefully consider granting waivers from that requirement in a treatment setting, on the grounds that review by an IRB for conformance with ethical principles designed for the research setting is not always necessary in a treatment context. For treatment protocols covering many patients, the IRB review requirement (or waiver therefrom) applies only once to the initial protocol, not to each patient that is added to it. Of course, FDA waiver of an IRB requirement would not preclude a local IRB from requiring physicians to obtain IRB review for all experimental procedures conducted in the institution.

When FDA does waive IRB review requirements, it may require as a condition of such waiver that the sponsor submit adequate assurance that the treatments use is to be conducted in conformity with all applicable requirements regarding the ethical conduct of an investigation. In particular, FDA may require the submission of sample informed consent forms to demonstrate that adequate and informed consent will be obtained. This is especially important when IRB review has been waived because IRB review is the chief means of assuring adequate informed consent of patients.

It should be emphasized that the treatment IND or treatment protocol is suitable only as a mechanism to obtain a drug that is not otherwise obtainable. The mechanism would not be appropriate as a means of obtaining a commercially available approved drug for a treatment use that is not described in the product's package insert. Such uses of marketed products, if within the practice of medicine, are beyond FDA's authority to require submission of an IND. The applicability of IND requirements to the use of marketed drugs is discussed elsewhere in this preamble.

Emergency Procedures

The need for an investigational drug may arise in an emergency situation that does not allow time for compliance with applicable IND submission requirements. The proposal would formally establish the mechanism now used for obtaining a drug in an emergency. The proposal would permit FDA to authorize shipment of a drug for a specified use before submission of an IND. Such requests would usually be made over the telephone. FDA's authorization would typically require the person who obtains the drug on an emergency basis to followup the initial request with a full written IND submission.

Administrative Actions on an IND

FDA proposes to describe in the regulations administrative actions the agency may take in reviewing an initial IND and in monitoring the progress of investigations that are conducted under an effective IND.

As noted in the introductory section of this preamble, under current requirements FDA has 30 days to review an initial IND submission. FDA's reviewers are asked to decide whether the information submitted in the application supports initiation of the proposed clinical investigations. If the reviewers find that some deficiency in the application justifies delaying the commencement of human studies, a "clinical hold" may be imposed instructing the sponsor not to begin the studies. The kinds of deficiencies that would justify a clinical hold are not described in the current regulations. Unless otherwise notified, a sponsor may begin human studies 30 days after FDA receives the IND.

Once clinical investigations begin, the principal mechanisms of further FDA regulation are deficiency letters, which point out specific technical problems in the application; clinical holds, which are orders to stop or limit specifically identified studies under an IND; and terminations, which are orders that prohibit all investigational activity under an IND.

Current regulations impose no obligations on FDA to explain actions taken with respect to an IND, provide no effective procedures for appealing decisions during the IND process, and fail to explain the regulatory significance of agency deficiency letters and other communications sent to the sponsor during the pendency of an IND. Also, current regulations concerning administrative actions do not describe the proper scope of FDA review during the different phases of the IND process. Therefore, FDA believes that a comprehensive revision and restatement of IND procedures and standards for administrative actions should be undertaken.

The proposal would attempt to remedy these omissions, among other ways, by specifying clinical hold and termination procedures that reflect the changing focus of FDA's concerns in reviewing IND's for different phases, by clarifying the regulatory status of FDA's communications to sponsors, and by codifying an appeals mechanism.

The proposal would also retain the 30-day period for review of initial IND submissions. FDA believes that the 30-day period imposes little if any delay on the drug development process while providing FDA with adequate time to fulfill the agency's responsibilities in monitoring and assessing the safety of proposed human studies. At the same time, FDA concludes that it is unnecessary to establish an affirmative approval mechanism for IND's, i.e., a mechanism under which a sponsor could only begin a study after receiving written notification from FDA. FDA believes the current mechanism has worked well and should not be changed.

1. *Deficiency letters.* Under current practice, FDA frequently sends letters to sponsors outlining deficiencies in the IND or requesting additional data or information. These "deficiency letters" may follow FDA review of the initial IND or a subsequent amendment, and the letters ae usually not accompanied by a "clinical hold" order. Accordingly, the regulatory status of such letters has been unclear, and some sponsors have apparently interpreted such letters as imposing regulatory "requirements." Under the proposal, the practice of sending deficiency letters to sponsors would be retained, but the regulatory status of these letters would be clarified. Specifically, the proposal states that such letters would be advisory only and would not require any action by sponsors, unless accompanied by a "clinical hold" order. FDA believes this provision should provide both sponsors and agency staff with clear notice of their rights and responsibilities regarding these communications.

2. *Clinical holds.* The proposal would define the standards for imposing a clinical hold during the different phases of the investigation. Standards for Phase 1 clinical holds would reflect FDA's focus on safety. Thus, a hold in Phase 1 could only be imposed if FDA found one of the following: (1) Human subjects would be exposed to an unreasonable and significant risk of illness or injury (without commensurate benefit to the subject); (2) the clinical investigators were not adequately qualified to conduct the investigation; (3) the investigator's brochure was misleading, erroneous, or materially incomplete; or (4) the IND did not contain enough information to assess the risks to human

subjects. This narrowed scope of review would mean that FDA could not impose a clinical hold on a proposed Phase 1 study on concluding that the study was poorly designed or without a proper scientific rationale, unless those deficiencies had a direct bearing on safety. The purpose of this standard is to give sponsors greater freedom to design, revise, and implement early clinical research, as long as patients are not put at risk. Phase 1 studies are almost never considered pivotol for marketing approval, so FDA's responsibility is met at this stage once safety is established. The agency estimates that these narrowed clinical hold criteria would reduce the number of commercial IND's placed on clinical hold by approximately 30 percent. In contrast, during Phases 2 and 3, FDA would be able to stop or delay a study not only for safety, but also if the agency found that the study was "clearly deficient in design to meet its stated objective." The purpose of this different standard is to eliminate the wasteful expenditure of resources by sponsors in undertaking major clinical studies which, on their face, are simply incapable of producing data to support marketing approval.

The proposal would make clear FDA's authority to impose a clinical hold, not only prior to the beginning of a study, but at any time during the course of a clinical investigation. The proposal would also establish procedures to standardize the imposition of clinical holds. First, a clinical hold could only be imposed following a decision by the director of the division that is responsible for reviewing the IND, and the division director would be required to give the sponsor a written explanation of the basis for the hold within 15 days. Second, the clinical hold order would specify whether the study may be commenced or resumed as soon as stated deficiencies are corrected or whether the study's resumption must await the responsible division director notifying the sponsor that the study may proceed. Finally, as described below, if all investigations under an IND remain under a clinical hold order for 1 year or more, FDA could place the IND on inactive status.

In the clinical hold area, as elsewhere, the proposed regulation stresses the agency's commitment to seek the resolution of problems through informal discussions and meetings before resorting to formal regulatory mechanisms. Thus, the proposal provides that whenever FDA believes that a clinical hold should be imposed, it would attempt within the 30 days to discuss and resolve the matter with the sponsor before imposing the hold.

3. *Termination of an IND.* The proposed revisions of the "terminations" provisions should be viewed as an extension of the proposed revisions regarding "clinical holds." As described above, a clinical hold is an order not to commence or continue a clinical study. The order is viewed as a temporary measure until the problems affecting the specific studies placed on clinical hold can be resolved. In contrast, a termination order is viewed with a greater sense of finality. It is an order that affects all studies being conducted under an IND. In general, an IND would not be terminated if FDA felt there was any real prospect of continuing the investigation. Historically, the termination provision has been used only rarely, but FDA believes it is a necessary sanction to permit FDA to exercise its responsibilities in monitoring adequately the IND process.

The proposal would restate the general grounds for termination of an IND contained in the current regulations, but would tailor the grounds to the specific phases of the investigation. during Phase 1, terminations would be limited to issues involving the safety of subjects or substantial noncompliance with the regulations. In addition to these grounds, the proposal would permit the agency to terminate an IND during Phase 2 and Phase 3 investigations if the plan or protocol were not reasonable as a bona fide scientific plan for determining whether the drug is safe and effective, or if there exists convincing evidence that drug is ineffective for the purpose for which it is being investigated. These latter two criteria (i.e., "not reasonable as a bona fide scientific plan" and "convincing evidence that the drug is ineffective") are expected to apply only in rare cases.

The proposal would retain the current procedures for terminating an IND. Under those procedures, when FDA proposes to terminate an IND, it first notifies the sponsor in writing and gives the sponsor an opportunity to correct any deficiencies or explain why it believes termination of the IND is unwarranted. The sponsor then has 30 days to provide a written response or request a conference with FDA to respond to the agency's proposal. Lacking any response, FDA will terminate the IND. If the sponsor provides a response that the agency finds unacceptable, it will give the sponsor an opportunity for a regulatory hearing under 21 CFR Part 16 of FDA's administrative practice and procedure regulations on the question of whether the IND should be terminated. If FDA's proposed grounds for termination are sustained, the IND is terminated. Following termination, the sponsor is required to discontinue all ongoing studies and properly dispose of supplies of the investigational drug. FDA will, in general, only initiate termination proceedings after first attempting to resolve differences informally or, when appropriate, through the clinical hold procedures described above.

Finally, the proposal would retain the provision in the current regulations that permit FDA to terminate an IND immediately if the agency concludes that continuation of an investigation presents a significant danger to the public or patient health. Although this procedure has only rarely been utilized, FDA believes it represents a valuable procedural complement to the other mechanisms available for ending studies conducted under an IND.

4. *Inactive status.* FDA proposes to establish an inactive status: (1) For IND's for which no subjects have been entered into clinical studies for a period of 2 years or more; or (2) for which all investigations under the IND have been on clinical hold for 1 year or more. Under the proposal, FDA could place an IND on inactive status on the request of the sponsor or on the agency's own initiative. If FDA acts on its own initative, it would first give the sponsor notice of the proposed action and an opportunity to show that clinical investigations under the IND are being conducted and therefore that the IND should remain active. No clinical studies would be permitted under an inactive IND, but neither would the sponsor be required to comply with the annual reporting requirement applicable to IND's. Resumption of clinical studies would require the submission of amendments describing the proposed investigations. Finally, the agency could terminate an IND that remains inactive for 5 years or more.

This change is intended to help FDA keep track of IND's that are no longer considered active and would also benefit drug sponsors who now make nonsubstantive submissions in the form of annual reports to IND's for which no clinical studies are ongoing or planned. Sponsors believe these submissions are necessary to prevent their applications from being considered abandoned, which under current regulations would make all data and information in the IND available for public disclosure unless extraordinary circumstances exist (see current 21 CFR 312.5(b) and 314.14(f)). This proposal would eliminate the need to submit those reports for

inactive IND's. FDA would presume an inactive IND to be in effect for purposes of the public disclosure of data and information in the IND.

The Pharmaceutical Manufacturers Association (PMA) Petitioned FDA to provide for an inactive status for IND's for which sponsors have discontinued clinical investigations. The PMA petition and this proposal are similar in that both would provide for a sponsor to request that an IND be considered inactive, both would eliminate the requirement for annual reports for inactive IND's, and both would protect trade secrets and confidential commercial and financial information from public disclosure.

FDA's proposal differs from the PMA petition, however, in several respects. First, under FDA's proposal, the agency could place an IND on inactive status without the sponsor's consent. The agency believes that this provision is necessary to keep government records current so that agency resources can appropriately be directed to IND's under which clinical investigations are actually being conducted. Second, under the proposal, to resume a study placed on inactive status, a sponsor would have to submit a protocol amendment and wait 30 days for FDA review, paralleling the procedure for initial IND's. FDA believes a 30-day pause before resumption of studies under an inactive IND is necessary because the general accumulation of scientific knowledge during the period of inactivity may affect the risk assessment of studies under the IND. Thus, a reassessment of the potential risks to subjects as well as the potential scientific usefulness of Phase 2 and Phase 3 studies is appropriate after a substantial period of inactivity.

5. *Request for reconsideration or clarification.* FDA recently adopted a new appeals process under which the sponsor of an NDA or IND can appeal a request or opinion from the division monitoring the application. This procedure, which is more fully described in a publicly available FDA Staff Manual Guide (NCDB 4820.5), was first outlined in the agency's proposal to revise its new drug and antibiotic application procedures (see 47 FR 46622, 46633–46634; October 19, 1982). Sponsors can use the procedure to appeal requests by agency employees for specific additional studies or information, requests to modify or delay a study, or unfavorable agency responses to sponsors' requests for waivers or special technical approaches to scientific problems. The procedure is marked by the sponsor's submission of a written request for reconsideration or clarification to the division responsible for reviewing the IND, the division's prompt response to the sponsor, and, if the division's response is not acceptable, automatic review of the issue by management of the National Center for Drugs and Biologics. FDA will attempt to issue a final decision within 60 days of a sponsor's initial request. The IND Rewrite would simply codify the applicability of this procedure to the IND process. This procedure has already been implemented for both NDA's and IND's through the staff manual guide noted above.

Meetings

This section describes the use of meetings to improve communications between FDA and sponsors of clinical investigations and thus to facilitate the drug development and approval process. FDA proposes to expand and codify its current practices with respect to meetings with IND sponsors during the course of clinical investigations and in preparation for submission of a marketing application. Although FDA encourages frank and open communication with sponsors throughout the drug development and approval process, it has found that discussions held at the end of Phase 2 of an investigation ("end-of-Phase 2" meetings) and meetings held before submission of a marketing application ("pre-NDA" meetings) are most helpful in facilitating drug development and marketing.

Under the proposal, any IND sponsor may request and obtain an end-of-Phase 2 meeting with reviewing officials, with a special emphasis on new chemical entities under development. FDA's current practice is to encourage end-of-Phase 2 meetings for new chemical entities offering major or modest therapeutic gains over existing drugs. (Type IA and IB drugs under the agency's classification system). FDA's success with these meetings has led it to conclude that the development of other drugs, especially other new chemical entities, would most likely benefit from such early consultation as well. Although other new chemical entities are classified as providing little or no therapeutic gain over existing drugs (Type IC), these products may still provide improved therapeutic benefits for some patients who do not respond well to available therapy. In addition, increase availability of similar drugs should help increase competition in the marketplace.

The primary objective of the end-of-Phase 2 meeting would be for FDA and the sponsor to reach an agreement on the overall plan for Phase 3 clinical investigations and the objectives and designs of particular studies. Minutes of the meeting would reflect the agreements reached. Unless a significant scientific development requires otherwise, the sponsor would be assured that studies performed in accordance with the agreements would be acceptable to FDA (in design and objectives) for purposes of an application for marketing approval.

FDA believes that the kind of collaborative planning that takes place in such meetings is one of the best means available for facilitating drug development without compromising the safety or effectiveness of marketed drugs. One of the greatest sources of delay in the review of marketing applications is when sponsors submit reports from "pivotal" studies that are found to have significant flaws in design. In this situation, prolonged discussions frequently follow on whether the studies are "adequate and well-controlled" and whether the results are scientifically credible. Sponsors, understandably, are dismayed at the prospect of having to re-do major studies, but FDA cannot approve a drug for marketing that does not meet the statutory standards. FDA's experience is that questions of study design can almost always be worked out and agreed upon—if the discussion takes place before the studies have been conducted. Accordingly, although increased availability of end-of-Phase 2 meetings will create more resource demands on the agency and on sponsors, FDA believes that resources spent increasing the efficiency of the drug development process are well worth spending.

The proposal would specifically provide that both sponsors and the agency may bring outside expert consultants to end-of-Phase 2 conferences. FDA has sought in the past to involve outside experts in end-of-Phase 2 meetings, where practicable, and the agency's experience has been that such expertise is often of considerable benefit in planning the design of Phase 3 studies. FDA, therefore, plans to continue this policy.

FDA also proposes to codify its procedures for "pre-NDA" meetings that are held to discuss new drug and antibiotic applications and biological product license applications. The agency has found these meetings to be useful in ensuring that marketing applications present data in a manner suitable for efficient agency review. "Pre-NDA" meetings are another mechanism

whereby advance planning can facilitate the drug review process.

Applicability of IND Requirements to Marketed Drugs

This section describes the applicability of IND requirements to marketed drugs. Specifically, the proposal: (1) Would clarify that the act does not regulate the "practice of medicine" so that a licensed physician may prescribe an approved drug for an unapproved indication; (2) would also clarify that the act does regulate "clinical investigations" using marketed drugs; but (3) would create a new category of clinical investigations using marketed drugs that would no longer require an IND.

Current regulations are silent on the act's applicability to the use of approved drugs for unapproved uses. This issue has caused considerable confusion both inside and outside the agency. In the Federal Register of August 15, 1972 (37 FR 16503), the agency proposed a regulation that would have put forth the legal status of approved labeling; although no final rule has been issued on this subject, the agency has continued to apply the principles set forth in the preamble to the 1972 proposal. In FDA's *Drug Bulletin* of April 1982, the agency sought to clarify and reiterate the position that the act does not regulate the "practice of medicine." Once a drug product has been approved for marketing, a physician may, in treating patients, prescribe the drug for uses not included in the drug's approved labeling. The primary legal constraints in that situation are State laws on medical practice and products liability law. The IND Rewrite proposal would codify the agency's longstanding position that the regulations do not apply to the "practice of medicine," though the proposal does not purport to define with specificity such practice in terms of the act.

A different issue arises when physicians, usually affiliated with academic institutions, seek to conduct "clinical investigations" using marketed drugs, either to look for new uses or to use the drug as a research tool. FDA's position has been, and continues to be, that such investigations are subject to section 505(i) of the act (21 U.S.C. 355(i)). Thus, the agency has received numerous IND's each year covering these types of studies. FDA, however, has reevaluated the utility of reviewing these IND's and has concluded that the agency's review of certain categories of them, as described below, is not necessary to assure patient protection. Accordingly, FDA proposes to exempt from the IND requirements of Part 312 clinical investigations using marketed drugs that meet the following two criteria: (1) The investigation does not involve a route of administration or dosage level or use in a patient population that significantly increases the risk associated with use of the drug product; (2) the investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use, nor intended to be used to support any other significant change in the advertising or labeling for the drug.

The first criterion embodies the view that, where a marketed drug is investigated in a way consistent with its approved labeling, FDA review is not needed to protect the safety of research subjects. The agency's approval of a new drug product for marketing is based on a substantial body of scientific information demonstrating the drug's safety in certain doses, routes of administration, and, sometimes, in certain patient populations. That information is conveyed to physicians through detailed professional labeling Administration of the drug under circumstances similar to those described in the approved labeling would not, therefore, be expected normally to produce any significant safety problems necessitating FDA review under the IND process.

FDA recognizes that the safety standard in the proposal contains an element of professional judgment in determining whether the conditions of the investigations "significantly increase" the risk associated with use of the drug. In applying this test, physicians should rely upon the contents of the approved labeling, reports in the medical literature, and their own experience in medical practice. For example, safety concerns necessitating submission of an IND would ordinarily arise where: (1) A drug is to be administered in a dosage many times greater than the labeled amount (new dosage level); (2) a drug approved for use in an oral dosage form is to be used in an intravaneous solution (new dosage form); or (3) an anticancer drug is to be used in patients with nonmalignant disease (new patient population). As an adjunct to these general criteria, FDA would also provide public notice when specific situations are identified that would require an IND.

The second criterion in the proposed regulation is aimed at helping ensure that investigations intended to be submitted to FDA for labeling or advertising changes are adequate in design to serve that purpose. This is the same reason the agency evaluates the design of Phase 2 and Phase 3 studies, and why FDA encourages close consultation with sponsors through participation in "End-of-Phase 2" conferences. As noted earlier, such review by FDA in advance adds considerable efficiency to the drug development process.

Persons conducting exempted studies would still be required to conform to all ethical principles applicable to the conduct of clinical investigations, including the statutory requirement for informed consent. Thus, a study's exemption under the proposal would be conditioned on a sponsor obtaining appropriate informed consent as well as the review and approval of a local IRB. Finally, the sponsor would still be prohibited from commercializing the investigation or promoting the product for its investigated use, except on specific approval by FDA.

The agency considered several alternatives to exempting such studies from IND submission requirements. For example, FDA considered requiring the submission to FDA of an "abbreviated IND" for this subset of uses. Such an IND would simply identify the investigational use the sponsor proposed to study and explain why the study met the criteria for exemption. This notification scheme would arguably permit FDA to play a more active role in regulating these investigations and would allow the agency, if a proposed study failed to meet the criteria for exemption, to stop it prior to its beginning. FDA is concerned, however, that such a system woud actually slow down the process because an abbreviated IND is unlikely to contain sufficient information to verify the criteria. Because reviewers are likely to ask for additional information and delay commencement of the studies, FDA does not consider this to be the best available option. The agency also considered expressly requiring IND's for these studies but, for the reasons stated above, FDA believes agency review is unnecessary to meet FDA's regulatory responsibilities.

The exempted group would include many, if not most, studies conducted by individual investigators in which marketed drugs are used as research tools or in exploratory therapeutic trials. The exemption would also apply to commercially sponsored studies if they fell into the exempted category. The agency would not accept IND's for exempt studies. FDA anticipates that there may be questions raised about the exempt status of certain kinds of investigations. FDA will provide assistance to interested persons who are

uncertain whether a proposed study falls under the terms of this exemption.

FDA believes that the exemption for studies of marketed drugs should significantly reduce administrative burdens placed on research conducted by individual investigators without compromising patient safety. FDA should also benefit because studies that would be exempted under the proposal constitute a significant fraction (over 15 percent) of all IND's received by FDA in a given year. Thus, review time and other staff time that are now spent on these IND's would be saved and redirected toward commercial IND's for new products under development, FDA reviews, and other review functions.

Responsibilities of Sponsors and Investigators

FDA proposes to summarize in the regulations the requirements concerning the responsibilities of sponsors and investigators under an IND. These provisions are intended to supplement more detailed requirements contained in FDA's proposed regulations defining the obligations of sponsor and monitors (42 FR 49612; September 27, 1977; proposed Part 52) and of clinical investigators (43 FR 35210; August 8, 1978; proposed Part 54). As noted earlier in this preamble, the IND proposal has been prepared on the assumption that sponsor/monitor and clinical investigator regulations will be made final either before, or at the same time as, the final IND Rewrite. Responsibilities of sponsors and/or clinical investigators are also contained in current FDA regulations on: (1) Informed consent (21 CFR Part 50), (2) institutional review boards (21 CFR Part 56), and (3) good laboratory practice for conducting nonclinical laboratory studies (21 CFR Part 58). To the extent that apparent inconsistencies may develop between the IND regulations and the bioresearch monitoring regulations, the bioresearch regulations would control and the IND regulations would be appropriately clarified when published in final form.

The IND proposal would retain current requirements for a sponsor to (1) select qualified investigators, (2) provide them with the information they need to conduct an investigation properly, (3) ensure proper monitoring of the investigation, (4) ensure that the investigation is conducted in accordance with the general investigational plan and protocols contained in the IND, (5) maintain an effective IND with respect to the investigation, and (6) ensure that FDA and all participating investigators are promptly informed of significant new safety information with respect to the drug. The proposal would also retain current requirements for an investigator to ensure: (1) That the investigation is conducted according to the investigator's statement that was provided to the sponsor, the investigational plan, and applicable FDA regulations; (2) the rights, safety, and welfare of subjects under the investigator's care are protected; and (3) that the drugs used in the investigation are kept under careful control.

One of the primary responsibilities of sponsors under an IND is to select investigators and a monitor who are qualified by training and experience to investigate the drug and monitor the investigations. In this regard the sponsor is required to obtain from each clinical investigator an investigator's statement containing information about the investigator, the facilities where the study will be conducted, and commitments by the investigator with respect to his or her involvement in the study. The sponsor is also required to obtain a curriculum vitae for each investigator and an outline of the plan of investigation.

Unlike most FDA regulations, the current content requirements for an investigator statement are contained in Form FDA–1572 (for investigators involved in clinical pharmacology) and Form FDA–1573 (for investigators involved in clinical trials). The forms, which are reprinted in the regulations, identify in detail the kinds of information the investigator must provide to the sponsor and contain specific commitments the investigator makes with respect to the investigation. The agency proposes to combine the forms into a single investigator statement Form FDA–1572 and to revise the form to make it simply a checklist of the investigator's submission. The agency would provide guidelines to help investigators compile necessary information and provide it to the sponsor.

As described more fully above, the sponsor would be required, as now, to provide each investigator with an investigator brochure containing the information the investigator needs to conduct the investigation properly. In addition, the sponsor is under a continuing obligation to keep each participating investigator informed about new information about the drug, particularly with respect to safety information and the drug's safe use. The important safety information should be communicated orally to investigators with a written followup.

Under the proposal, a sponsor would continue to monitor an investigation by securing compliance of noncomplying investigators with the investigational plan and ending an investigator's participation if he or she refuses to comply with the plan. In addition, the sponsor must monitor the progress of investigations, evaluate safety and effectiveness information, and make reports to FDA regarding adverse drug experiences. All records of the investigation would of course be available for inspection by authorized Federal employees. If a sponsor determines that an adverse drug effect presents an unreasonable and significant risk to subjects, the sponsor must (1) discontinue the investigation and notify FDA and all investigators, (2) dispose of all stocks of the drug, and (3) provide FDA with a full report of the actions taken. Although current regulations require that the sponsors take this action promptly, the proposal would require a sponsor to discontinue an investigation as soon as possible, but in no event later than 5 working days after determining it should be discontinued.

Miscellaneous Provisions

1. *Sale of investigational drugs.* The proposal would retain, essentially unchanged, the current provisions prohibiting promotion and commercialization of investigational drugs. The proposal would also retain the current policy of not permitting sale of an investigational drug unless a full and satisfactory explanation is given why the sale should not be regarded as commercializing the drug. However, while this policy applies to sale of any investigational drug, the procedure for implementing the policy is different for investigational biological products than it is for investigational new drugs and antibiotics. For biologics, sale is not permitted until the sponsor is notified of FDA's approval of the sale. With respect to new drugs and antibiotics, there is no written current policy, and therefore the issue is subject to differing interpretations and applications, although in practice FDA usually does make affirmative decisions on whether to permit sale. The proposal would extend the procedure for sale of biological products to all investigational drugs so that no sale would be permitted except upon written approval of the Director, National Center for Drugs and Biologics. Centralizing these decisions in one individual would ensure uniform application of the agency's policy in this area.

2. *Imports and exports.* FDA proposes to codify its current policy on imports and exports of investigational new drugs. The Federal Food, Drug, and

Cosmetic (the act) prohibits, under sections 301(d) and 505(a) (21 U.S.C. 331(d) and 355(a)), the introduction or delivery for introduction into interstate commerce of any new drug without an approved application under section 505(b) or an exemption under section 505(i). That prohibition extends to imports and exports of unapproved new drugs under the act's definition of the term "interstate commerce" (section 201(b)) (21 U.S.C. 321(b)). Thus, an unapproved new drug may not be imported into, or exported from, the United States unless it is subject to an exemption provided by FDA for an investigational new drug.

The proposal would simplify the agency's regulations governing imports by requiring an investigational new drug offered for importation into the United States to be subject to an effective IND and require the consignee within the United States to be either the sponsor of the IND or an investigator named in the IND. If the sponsor did not reside in the United States, the sponsor would be required to designate a domestic agent to act on behalf of the sponsor.

The proposal would retain the agency's current policies on exports of an investigational new drug by providing that such drug may be exported from the United States if an IND is in effect for it and each person to whom it is exported is an investigator named in the IND. The proposal would also modify the procedures under which FDA may authorize export of an investigational new drug that is not subject to an IND. Currently, requests for export under these procedures may only be processed through the Department of State.

The proposal would streamline this process by permitting these requests to be submitted directly to FDA by an authorized official of the importing foreign government. As an alternative procedure, the proposal would also permit requests to be submitted by an official of the company that proposes to export the drug. In either case, FDA will authorize shipment only if it is satisfied that the drug is appropriate for investigational use in human subjects, that the drug will be used for investigational purposes only, and that the drug may legally be used by the consignee in the importing country. The amount of information needed to satisfy these criteria will vary depending on the nature of the drug and FDA's prior familiarity with it.

FDA will coordinate export authorization with the appropriate governmental officials of the importing countries. As in the past, FDA will give considerable deference to letters by foreign governments specifically requesting shipment of the drug into their country. Where the request is made by the exporter, FDA will notify the foreign government of any export authorizations that are made.

Finally, the agency emphasizes that these procedures do not permit export of an investigational drug for commercial marketing or for use in routine medical practice.

3. *Foreign clinical studies.* The proposal would retain current policy on FDA's acceptance for IND purposes of foreign clinical studies not conducted under an IND. The regulation itself has been redrafted to provide greater clarity. FDA accepts well-designed and well-conducted investigational studies that are performed by qualified investigators in accordance with ethical principles acceptable to the world community. Studies meeting these criteria may be used to support clinical investigations in the United States as well as subsequent marketing approval. Marketing approval of a new drug or antibiotic drug based solely on foreign clinical data, however, would be governed by the agency's regulations on new drug applications in Part 314 (see the proposal in 47 FR 46622, 46642–46644, and 46655; October 19, 1982).

4. *Public availability of data and information in an IND.* FDA proposes no substantive change in the specific regulations applicable to the availability for public disclosure of data and information in an IND. (Although, as noted above, FDA does propose to treat an IND on inactive status as an active IND for purposes of the public disclosure of data and information.) The proposal would retain the current provisions which (i) prohibit FDA disclosure of the existence of an IND, (ii) apply to IND's the same provisions for public release of data and information in a new drug application (NDA) under Part 314, and (iii) specifically provide for the disclosure to an individual patient who received an investigational new drug of a copy of any adverse reaction report relating to the use of the drug in that individual.

5. *Address for correspondence.* FDA proposes a new section in the regulations to identify the appropriate agency offices to which IND's should be sent. The regulation would also require the outside wrapper of each IND submission to identify the submission (for example, as the original IND submission, protocol amendment, information amendment, adverse drug experience report, or annual report).

6. *Guidelines.* This section simply states that the agency prepares guidelines to help persons comply with the regulations. As stated in § 10.90(b), guidelinnes do not establish legal requirements but a person may be assured that by following an agency guideline his or her submission will be in a form acceptable to the agency. A person may also choose to use alternative procedures or standards even though they are not provided for in a guideline. A person who chooses to use alternative procedures or standards may discuss the matter in advance with FDA to prevent an expenditure of money and effort on work that may later be found unacceptable. The agency also proposes to establish and make publicly available a list of guidelines that apply to the IND regulations.

7. *Use in laboratory research animals or in vitro tests.* Although an IND is not required, the agency proposes to retain, with some editorial changes, its current regulations governing the proper labeling and control of investigational new drugs intended solely for use in laboratory research animals, or for tests in vitro.

Environmental Impact

The agency has determined under 21 CFR 25.24(b)(17) (proposed December 11, 1979; 44 FR 71742) that this proposed action is of a type that does not individually or cumulatively have a significant impact on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

Paperwork Reduction Act of 1980

This proposed rule contains a number of information collection requirements. As required by section 3504(h) of the Paperwork Reduction Act of 1980, FDA has submitted a copy of this proposed rule to the Office of Management and Budget (OMB) for its review of these information collection requirements. Other organizations and individuals desiring to submit comments on the information collection requirements should direct them to FDA's Dockets Management Branch (address above) and to the Office of Information and Regulatory Affairs, OMB, New Executive Office Building (Rm. 3208), Washington, DC 20503, ATTN: Richard Eisenger.

FDA proposes that the final regulation be effective 60 days after its date of publication in the **Federal Register.**

List of Subjects in 21 CFR Part 312

Drugs, Medical research.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 501, 502, 503, 505, 506, 507, 701, 52 Stat. 1049–1053

as amended, 1055–1056 as amended, 55 Stat. 851, 59 Stat. 463 as amended (21 U.S.C. 351, 352, 353, 355, 356, 357, 371)) and the Public Health Service Act (sec. 351, 58 Stat. 702 as amended (42 U.S.C. 262)) and under 21 CFR 5.11 as revised (see 47 FR 16010; April 14, 1982), it is proposed that Part 312 be revised to read as follows:

PART 312—INVESTIGATIONAL NEW DRUG APPLICATION

Subpart A—General Provisions

Subpart B—Investigational New Drug Application (IND)

Subpart C—Administrative Actions

Subpart D—Responsibilities of Sponsors and Investigators

Subpart E—Miscellaneous

Subpart F—Drugs for Investigational Use in Laboratory Research Animals or In Vitro Tests

Authority: Secs. 501, 502, 503, 505, 506, 507, 701, 52 Stat. 1049–1053 as amended, 1055–1056 as amended, 55 Stat. 851, 59 Stat. 463 as amended (21 U.S.C. 351, 352, 353, 355, 356, 357, 371); sec. 351, 58 Stat. 702 as amended (42 U.S.C. 262).

Subpart A—General Provisions

§ 312.1 Scope.

(a) This part contains procedures and requirements governing the use of investigational new drugs, including procedures and requirements for the submission to, and review by, the Food and Drug Administration of investigational new drug applications (IND's). An investigational new drug for which an IND is in effect in accordance with this part exempts the drug from the premarketing approval requirements that are otherwise applicable and permits the drug to be shipped lawfully for the purpose of conducting clinical investigations of that drug.

(b) References in this part to regulations in the Code of Federal Regulations are to Chapter I of Title 21, unless otherwise noted.

§ 312.2 Applicability.

(a) Except as provided in this section, this part applies to all clinical investigations of drugs that are subject to section 505 or 507 of the Federal Food, Drug, and Cosmetic Act or to the licensing provisions of the Public Health Service Act (58 Stat. 632, as amended (42 U.S.C. 201 et seq.)).

(b)(1) *Exemptions.* The following categories of drugs are exempt from the requirements of this part:

(i) a lawfully marketed drug product used in a clinical investigation, if all the following apply:

(*a*) The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the advertising or labeling for the drug;

(*b*) The investigation does not involve a route of administration or dosage level or use in a patient population that significantly increases the risks associated with use of the drug product;

(*c*) The investigation is conducted in compliance with the requirements for institutional review set forth in Part 56 and with the requirements for informed consent set forth in Part 50; and

(*d*) The investigation is conducted in compliance with the requirements of § 312.7.

(ii) A biological drug intended for in vitro diagnostic use if:

(*a*) It is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure, and

(*b*) The investigational drug is shipped in compliance with §312.160.

(iii) A drug intended solely for tests in laboratory research animals, if shipped in accordance with § 312.160.

(2) FDA will not accept an application for an investigation that is exempt under the provisions of paragraph (b)(1) of this section.

(c) For the applicability of this part to in vivo bioavailability studies in humans, see § 320.31.

(d) This part does not apply to the use in the practice of medicine for an unlabeled indication of a new drug or antibiotic drug product approved under Part 314 or of a licensed biological product.

(e) FDA may, on its own initiative, issue guidance on the applicability of this part to particular investigational uses of drugs. On request, FDA will advise on the applicability of this part to a planned clinical investigation.

§ 312.3 Definitions and interpretations.

(a) The definitions and interpretations of terms contained in section 201 of the act apply to those terms when used in this part.

(b) The following definitions of terms also apply to this part:

"Act" means the Federal Food, Drug, and Cosmetic Act (sections 201–902, 52 Stat. 1040 et seq., as amended (21 U.S.C. 301–392)).

"Clinical investigation" means any experiment in which an investigational new drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice.

"FDA" means the Food and Drug Administration.

"IND" means an investigational new drug application.

"Investigational new drug" means a new drug, antibiotic drug, or biological drug (including a biological product that is used in vitro for diaganostic purposes) that: is not marketed under an approved marketing application; or is a marketed drug that is used for any purpose or in any way other than that described in its labeling, except when such use is carried out by a licensed practitioner in

the course of medical practice. The terms "investigational drug" and "investigational new drug" are deemed to be synonymous for purposes of this part.

"Investigator" means an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or dispensed to a subject). In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team.

"Marketing application" means an application for a new drug submitted under section 505(b) of the act, a request to provide for certification of an antibiotic submitted under section 507 of the act, or a product license application for a biological product submitted under the Public Health Service Act.

"Sponsor" means a person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization or other organization. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators.

"Sponsor-Investigator" means an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. The term does not include any person other than an individual. The requirements applicable to a sponsor-investigator under this part include both those applicable to an investigator and a sponsor.

"Subject" means a human who participates in an investigation, either as a recipient of the investigational new drug or as a control. A subject may be a healthy human or a patient with a disease.

§ 312.6 Labeling of an investigational new drug.

(a) The immediate package of an investigational new drug intended for human use shall bear a label with the statement "Caution: New Drug—Limited by Federal (or United States) law to investigational use."

(b) The label or labeling of an investigational new drug shall not bear any statement that is false or misleading in any particular and shall not represent that the investigational new drug is safe or effective for the purposes for which it is being investigated.

§ 312.7 Promotion and sale of investigational drugs.

(a) *Promotion of an investigational new drug.* A sponsor or investigator, or any person acting on behalf of a sponsor or investigator, shall not represent in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug. This provision is not intended to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media: Rather, its intent is to restrict promotional claims of safety or effectiveness of the drug for a use for which it is under investigation and to preclude commercialization of the drug before it is approved for commercial distribution.

(b) *Commercial distribution of an investigational new drug.* A sponsor shall not commercially distribute or test market an investigational new drug.

(c) *Prolonging an investigation.* A sponsor shall not unduly prolong an investigation, but shall submit a marketing application for the drug, with reasonable promptness after finding that the results of the investigation appear to establish sufficient data to support a marketing application, or within 60 days of receipt of a request for such application by FDA. If the sponsor determines that the data obtained will support a marketing application, the sponsor shall promptly discontinue the investigation and withdraw the IND.

(d) *Sale of an investigational drug.* The sale of an ivestigational new drug is not permitted except upon the written approval of the Director of the National Center for Drugs and Biologics. To obtain approval for the sale of a drug, the sponsor shall submit a full written explanation why sale is required and why the sale should not be regarded as the commercialization of an investigational drug. No sale will be permitted except in the context of an acceptable investigation.

§ 312.10 Waivers.

(a) A sponsor may request FDA to waive any applicable requirement under this part. A waive request may be submitted either in an initial IND or in an information amendment to an IND. In an emergency, a request may be made by telephone or other rapid communication means. A waiver request is required to contain at least one of the following:

(1) An explanation why the sponsor's compliance with the requirement is unnecessary or cannot be achieved;

(2) A description of an alternative submission or course of action that satisfies the purpose of the requirement; or

(3) Other information justifying a waiver.

(b) FDA may grant a waiver if it finds that the sponsor's noncompliance would not pose a significant and unreasonable risk to human subjects of the investigation and that one of the following is met:

(1) The sponsor's compliance with the requirement is unnecessary for the agency to evaluate the application, or compliance cannot be achieved;

(2) The sponsor's proposed alternative satisfies the requirement; or

(3) The applicant's submission otherwise justifies a waiver.

Subpart B—Investigational New Drug Application (IND)

§ 312.20 Requirement for an IND.

(a) A sponsor shall submit an IND to FDA if the sponsor intends to conduct a clinical investigation with an investigational new drug that is subject to § 312.2(a).

(b) A sponsor shall not begin a clinical investigation subject to § 312.2(a) until the investigation is subject to an effective IND in accordance with § 312.40.

§ 312.21 Phases of an investigation.

An IND may be submitted for one or more phases of an investigation. The clinical investigation of a previously untested drug is generally divided into three phases. Although in general the phases are conducted sequentially, they may overlap. These three phases of an investigation are as follows:

(a) *Phase 1.* (1) Phase 1 includes the initial introduction of an investigational new drug into humans. Phase 1 studies are typically closely monitored and may be conducted in patients or normal volunteer subjects. These studies are designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. During Phase 1, sufficient information about the drug's pharmacokinetics and pharmacological effects should be obtained to permit the design of well-controlled, scientifically valid, Phase 2 studies. The total number of subjects and patients included in Phase 1 studies varies with the drug, but is generally in the range of 20 to 80.

(2) Phase 1 studies also include studies of drug metabolism, structure-activity relationships, and mechanism of action in humans, as well as studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes.

(b) *Phase 2.* Phase 2 includes the controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks associated with the drug. Phase 2 studies are typically well controlled, closely monitored, and conducted in a relatively small number of patients, usually involving no more than several hundred subjects.

(b) *Phase 3.* Phase 3 studies are expanded controlled and uncontrolled trials. They are performed after preliminary evidence of effectiveness of the drug has been established, and are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling. Phase 3 studies usually include from several hundred to several thousand subjects.

§ 312.22 General principal of the IND submission.

(a) FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, and, in Phase 2 and 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety. Therefore, although FDA's review of Phase 1 submissions will focus on assessing the safety of Phase 1 investigations, FDA's review of Phases 2 and 3 submissions will also include an assessment of the scientific quality of the clinical investigation and the likelihood that the investigations will yield data capable of meeting statutory standards for marketing approval.

(b) The amount of information on a particular drug that must be submitted in an IND to assure the accomplishment of the objectives described in paragraph (a) of this section depends upon such factors as the novelty of the drug, the extent to which it has been studied previously, the known or suspected risks, and the developmental phase of the drug.

(c) The central focus of the first IND submission should be on the general investigational plan and the protocols for specific human studies. Subsequent amendments to the IND that contain new or revised protocols should build logically on previous submissions and should be supported by additional information including the results of animal toxicology studies or other human studies as appropriate. Annual reports to the IND should serve as the focus for reporting the status of studies being conducted under the IND and should update the general investigational plan for the coming year. To aid communication and minimize paperwork, information and data in IND's should, with some exceptions, be submitted only in summary form.

(d) The IND format set forth in § 312.23 should be followed routinely by sponsors in the interest of fostering an efficient review of applications. Sponsors are expected to exercise considerable discretion, however, regarding the contest of information submitted in each section, depending upon the kind of drug being studied and the nature of the available information. Section 312.23 outlines the information needed for a commercially sponsored IND for a new molecular entity. A sponsor-investigator who uses, as a research tool, an investigational new drug that is already subject to a manufacturer's IND should follow the same general format, but ordinarily may refer to the manufacturer's IND in providing the technical information supporting the proposal clinical investigation. A sponsor-investigator who uses an investigational drug not subject to a manufacturer's IND is ordinarily required to submit all technical information supporting the IND, unless, such information may be referenced from the scientific literature.

§ 312.23 IND content and format.

(a) A sponsor who intends to conduct a clinical investigation subject to this part shall submit an "Investigational New Drug Application" (IND) including, in the following order:

(1) *Cover sheet (Form FDA–1571).* A cover sheet for the application containing the following:

(i) The name, address, and telephone number of the sponsor, the date of the application, and the name of the investigational new drug.

(ii) Identification of the phase or phases of the clinical investigation to be conducted.

(iii) A commitment not to begin clinical investigations until an IND covering the investigations is in effect.

(iv) A commitment that an Institutional Review Board (IRB) that complies with the requirements set forth in Part 56 will be responsible for the initial and continuing review and approval of each of the studies in the proposed clincial investigation, that investigators will report to the IRB all proposed changes in the research activity and all unanticipated problems involving risks to human subjects or others, and that investigators will not make any deviations from the research plan without IRB approval, except where necessary to eliminate apparent immediate hazard to human subjects.

(v) A commitment to conduct the investigation in accordance with all other applicable regulatory requirements.

(vi) The name and title of the person responsible for monitoring the conduct and progress of the clinical investigations.

(vii) If the sponsor is not a sponsor-investigator, the name and title of the individual responsible for evaluating adverse reactions or other evidence of risk when such information is received from the clinical investigators.

(vii) The signature of the sponsor or the sponsor's authorized representative. If the person signing the application does not reside or have a place of business within the United States, the IND is required to contain the name and address of, and be countersigned by, an attorney, agent, or other authorized official who resides or maintains a place of business within the United States.

(2) *A table of contents.*

(3) *Introductory statement.* (i) A brief introductory statement giving the name of the drug and all active ingredients, the drug's pharmacological class, the structural formula of the drug (if known), the formulation of the dosage form(s) to be used, the route of administration, and the broad objectives and planned duration of the proposed clinical investigation(s).

(ii) A brief summary of previous human experience with the drug, with reference to other IND's if pertinent, and to investigational or marketing experience in other countries that may be relevent to the safety of the proposed clinical investigation(s).

(iii) If the drug has been withdrawn from investigation or marketing in any country for any reason related to safety or effectiveness, identification of the country(ies) where the drug was withdrawn and the reasons for the withdrawal.

(4) *General investigational plan.* A brief description of the overall plan for investigating the drug product, including: (i) The rationale for the drug or the research study; (ii) the indication(s) to be studied; (iii) the general approach to be followed in evaluating the drug; (iv) the kinds of clinical trials to be conducted in the first year following the

submission; (v) the estimated number of patients to be given the drug in those studies, and (vi) any special risks anticipated on the basis of the toxicological data in animals or prior studies in humans with the drug or related drugs.

(5) *Investigator's brochure.* If required under § 312.55, a copy of the investigator's brochure, containing the following information.

(i) A brief description of the drug substance and the formulation, including the structural formula, if known.

(ii) A summary of the pharmacological and toxicological effects of the drug in animals and, to the extent know, in humans.

(iii) A summary of the pharmacokinetics and biological disposition of the drug in animals and, if known, in humans.

(iv) A summary of information relating to safety and effectiveness in humans obtained from prior clinical studies. (Reprints of published articles on such studies may be appended when useful.)

(v) A description of possible risks and side effects to be anticipated on the basis of prior experience with the drug under investigation or with related drugs, and of precautions or special monitoring to be done as part of the investigational use of the drug.

(6) *Protocols.* (i) A protocol for each planned study. In general, protocols for Phase 1 studies may be less detailed and more flexible than protocols for Phase 2 and 3 studies. Phase 1 protocols should be directed primarily at providing an outline of the investigation—an estimate of the number of patients to be involved, a description of safety exclusions, and a description of the dosing plan including duration, dose, or method to be used in determining dose—and should specify in detail only those elements of the study that are critical to safety, such as necessary monitoring of vital signs and blood chemistries. Modifications of the experimental design of Phase 1 studies that do not affect critical safety assignments are required to be reported to FDA only in the annual report.

(ii) In Phases 2 and 3, detailed protocols describing all aspects of the study should be submitted. A protocol for a Phase 2 or 3 investigation should be designed in such a way that, if the sponsor anticipates that some deviation from the study design may become necessary as the investigation progresses, alternatives or contingencies to provide for such deviation are built into the protocols at the outset. For example, a protocol for a controlled short-term study might include a plan for an early crossover of nonresponders to an alternative therapy.

(iii) A protocol is required to contain the following, with the specific elements and detail of the protocol reflecting the above distinctions depending on the phase of study:

(*a*) A statement of the objectives and purpose of the study.

(*b*) The name and address and curriculum vitae of each investigator, and the name of each subinvestigator (e.g., research fellow, resident) working under the supervision of the investigators; the name and address of the research facilities to be used; and the name and address of each reviewing Institutional Review Board.

(*c*) The criteria for patient selection and for exclusion of patients and an estimate of the number of patients to be studied.

(*d*) A description of the design of the study, including the kind of control group to be used, if any, and a description of methods to be used to minimize bias on the part of subjects, investigators, and analysts.

(*e*) The method for determining the dose(s) to be administered, the planned maximum dosage, and the duration of individual patient exposure to the drug.

(*f*) A description of the observations and measurements to be made to fulfill the objectives of the study.

(*g*) A description of clinical procedures, laboratory tests, or other measures to be taken to monitor the effects of the drug in human subjects and to minimize risk.

(7) *Chemistry, manufacturing, and control information.* (i) As appropriate for the particular investigations covered by the IND, a section describing the composition, manufacture, and control of the drug substance and the drug product. Although in each phase of the investigation sufficient information is required to be submitted to assure the proper identification, quality, purity, and strength of the investigational drug, the amount of information needed to make that assurance will vary with the phase of the investigation, the proposed duration of the investigation, the dosage form, and the amount of information otherwise available. FDA recognizes that modifications to the method of preparation of the new drug substance and dosage form and changes in the dosage form itself are likely as the investigation progresses. Therefore, the emphasis in an initial Phase 1 submission should generally be placed on the identification and control of the raw materials and the new drug substance. Final specifications for the drug substance and drug product are not expected until the end of the investigational process.

(ii) It should be emphasized that the amount of information to be submitted depends upon the scope of the proposed clinical investigation. For example, although stability data are required in all phases of the IND to demonstrate that the new drug substance and drug product are within acceptable chemical and physical limits for the planned duration of the proposed clinical investigation, if very short-term tests are proposed, the supporting stability data can be correspondingly limited.

(iii) As drug development proceeds and as the scale of production is changed from the pilot-scale production appropriate for the limited initial clinical investigations to the larger-scale production needed for expanded clinical trials, the sponsor should submit information amendments to supplement the initial information submitted on the manufacturing and control processes with information appropriate to the expanded scope of the investigation.

(iv) Reflecting the distinctions described in this paragraph (a)(7), and based on the phase(s) to be studied, the submission is required to contain the following:

(*a*) *Drug substance.* A description of the drug substance, including its physical, chemical, or biological characteristics; the name and address of its manufacturer; the general method of preparation of the drug substance; the acceptable limits and analytical methods used to assure the identity, potency, quality, and purity of the drug substance; and information sufficient to support stability of the drug substance during the toxicological studies and the planned clinical studies. Reference to the current edition of the U.S. Pharmacopeia and the National Formulary may be made to satisfy relevant requirements in this paragraph.

(*b*) *Drug product.* A list of all components, whic may include reasonable alternates for inactive compounds, used in the manufacture of the investigational drug product, including both those components intended to appear in the drug product and those which may not appear but which are used in the manufacturing process, and, where applicable, the quantitative composition of the investigational drug product, including any reasonable variations that may be expected during the investigational stage; the name and address of the drug product manufacturer; a brief general description of the manufacturing and packaging procedure as appropriate for the product; the acceptable limits and analytical methods used to assure the identity, strength, quality, and purity of

the drug product; and information sufficient to assure the product's stability during the planned clinical studies. Reference to the current edition of the U.S. Pharmacopeia and the National Formulary may be made to satisfy relevant requirements in this paragraph.

(c) *Labeling.* A copy of all labels and labeling to be provided to each investigator.

(d) *Environmental impact analysis report.* If requestd by FDA, environmental impact analysis report under § 25.1 analyzing the environmental impact of the manufacturing process and the ultimate use of the drug product.

(8) *Pharmacology and toxicology information.* Adequate information about pharmacological and toxicological studies of the drug involving laboratory animals or in vitro, on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations. The kind, duration, and scope of animal and other tests required varies with the duration and nature of the proposed clinical investigations. Guidelines are available from FDA that describe ways in which these requirements may be met. Such information is required to include the identification and qualifications of the individuals who evaluated the results of such studies and concluded that it is reasonably safe to begin the proposed investigations and a statement of where the investigations were conducted and where the records are available for inspection. As drug development proceeds, the sponsor is required to submit informational amendments, as appropriate, with additional information pertinent to safety.

(i) *Pharmacology and drug disposition.* A section describing the pharmacological effects and mechanism(s) of action of the drug in animals, and information on the absorption, distribution, metabolism, and excretion of the drug, if known.

(ii) *Toxicology. (a)* An integrated summary of the toxicological effects of the drug in animals and in vitro. Depending on the nature of the drug and the phase of the investigation, the description is to include the results of acute, subacute, and chronic toxicity tests; tests of the drug's effects on reproduction and the developing fetus; any special toxicity test related to the drug's particular mode of administration or conditions of use (e.g., inhalation, dermal, or ocular toxicology); and any in vitro studies intended to evaluate drug toxicity.

(b) For each toxicology study that is intended primarily to support the safety of the proposed clinical investigation, a full tabulation of data suitable for detailed review.

(iii) For each toxicology study submitted to support the safety of a proposed clinical study that was not conducted in compliance with Part 58 relating to good laboratory practices, a description of each difference between the practices used in the study and those required under Part 58.

(9) *Previous human experience with the investigational drug.* A summary of previous human experience, if any, with the investigational drug. The information is required to include the following:

(i) If the investigational drug has been investigated or marketed previously, either in the United States or other countries, detailed information about such experience that is relevant to the safety of the proposed investigation or to the investigation's rationale. If the drug has been the subject of controlled trials, detailed information on such trials that is relevant to an assessment of the drug's effectiveness for the proposed investigational use(s) should also be provided. Any published material that is relevant to the safety of the proposed investigation or to an assessment of the drug's effectiveness for its proposed investigational use should be provided in full. Published material that is less directly relevant may be supplied by a bibliography.

(ii) If the drug is a combination of drugs previously investigated or marketed, the information required under paragraph (a)(9)(i) of this section should be provided for each component.

(iii) If the drug has been marketed outside the United States, a list of the countries in which the drug has been marketed and a list of the countries in which the drug has been withdrawn from marketing for reasons potentially related to safety or effectiveness.

(10) *Additional information.* In certain applications, as described below, information on special topics may be needed. Such information shall be submitted in this section as follows:

(i) *Drug dependence and abuse potential.* If the drug is a psychotropic substance or otherwise has abuse potential, a section describing relevant clinical studies and experience and studies in test animals.

(ii) *Radioactive drugs.* If the drug is a radioactive drug, sufficient data from animal or human studies to allow a reasonable calculation of radiation-absorbed dose to the whole body and critical organs upon administration to a human subject. Phase 1 studies of radioactive drugs must include studies which will obtain sufficient data for dosimetry calculations.

(iii) *Other information.* A brief statement on any other information that would aid evaluation of the proposed clinical investigations with respect to their safety or their design and potential as controlled clinical trials to support marketing of the drug.

(11) If requested by FDA, any other relevant information needed for review of the application.

(b) *Information previously submitted.* The sponsor ordinarily is not required to resubmit information previously submitted, but may incorporate the information by reference. A reference to information submitted previously must identify the file by name, reference number, volume, and page number where the information can be found. A reference to information submitted to the agency by a person other than the sponsor is required to contain a written statement that authorizes the reference and that is signed by the person who submitted the information.

(c) *Material in a foreign languoge.* The sponsor shall submit an accurate and complete English translation of each part of the IND that is not in English. The sponsor shall also submit a copy of each original literature publication for which an English translation is submitted.

(d) *Number of copies.* The sponsor shall submit an original and two copies of all submissions to the IND file, including the original submission and all amendments and reports.

§ 312.30 Protocol amendments.

Once an IND is in effect, a sponsor shall amend it as needed to ensure that the clinical investigations are conducted according to protocols included in the application. This section sets forth the provisions under which new protocols may be submitted and changes in previously submitted protocols may be made.

(a) *New protocol.* Whenever a sponsor intends to conduct a study that is not covered by a protocol already contained in the IND, the sponsor shall submit to the IND a protocol amendment containing the protocol for the study. Such study may begin provided two conditions are met: (1) The sponsor has submitted the protocol to FDA for its review; and (2) the protocol has been approved by the institutional review board (IRB) with responsibility for review and approval of the study in accordance with the requirements of Part 56. The sponsor may comply with these two conditions in either order.

(b) *Changes in a protocol.* A sponsor shall submit a protocol amendment describing any change in a Phase 1 protocol that significantly affects the safety of subjects or any change in a Phase 2 or 3 protocol that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study. Such change may be made after the sponsor has submitted the amendment to the IND following completion of review of the change by the IRB that is responsible for review and approval of the study that is the subject of the protocol. Examples of changes requiring an amendment under this paragraph include:

(1) Any increase in drug dosage or duration of exposure of individual subjects to the drug beyond that in the current protocol, or any significant increase in the number of subjects under study.

(2) Any significant change in the design of a protocol (such as the addition or dropping of a control group).

(3) The addition of a new test or procedure that is intended to improve monitoring for, or reduce the risk of, a side effect or adverse event; or the dropping of a test intended to monitor safety.

(c) *New investigator.* A sponsor shall submit a protocol amendment when a new investigator is added to carry out a previously submitted protocol, except that a protocol amendment is not required when a licensed practitioner is added in the case of a treatment protocol under § 312.34. The sponsor shall notify FDA of the new investigator within 30 days of the investigator being added.

(d) *Content and format.* A protocol amendment is required to be prominently identified as such (i.e., "Protocol Amendment: New Protocol", "Protocol Amendment: Change in Protocol", or "Protocol Amendment: New Investigator"), to be serially numbered, and to contain the following:

(1)(i) In the case of a new protocol, a copy of the new protocol and a description of how it differs from previous protocols.

(ii) In the case of a change in protocol, a brief description of the change and reference (date and number) to the submission that contained the protocol.

(iii) In the case of a new investigator, the investigator's name and qualifications to conduct the investigation.

(2) Reference to the specific information in the IND or in a concurrently submitted information amendment to the IND that the sponsor relies on to support the new or amended protocol. If the reference is made to supporting information already in the IND, the sponsor shall identify by name, reference number, volume, and page number the location of the information.

(3) If the sponsor desires FDA to comment on the submission, a request for such comment and the specific questions FDA's response should address.

(e) *When submitted.* A sponsor shall submit a protocol amendment for a new protocol or a change in protocol before its implementation. Protocol amendments to add a new investigator or to provide additional information about investigators may be grouped and submitted at 30-day intervals. When several submissions of new protocols or protocol changes are anticipated during a short period, the sponsor is encouraged, to the extent feasible, to include these all in a single submission.

§ 312.31 Information amendments.

(a) *Requirement for information amendment.* A sponsor shall report in an information amendment essential information on the IND that is not within the scope of a protocol amendment, IND safety reports, or annual report. Examples of information requiring an information amendment include:

(1) New toxicology, chemistry, or other technical information; or

(2) A report regarding the discontinuance of a clinical investigation.

(b) *Content and format of an information amendment.* An information amendment is required to bear prominent identification of its contents (eg., "Information Amendment: Chemistry, Manufacturing, and Control"), to be numbered serially by discipline, and to contain the following:

(1) A statement of the nature and purpose of the amendment.

(2) An organized submission of the data in a format appropriate for scientific review.

(3) If the sponsor desires FDA to comment on an information amendment, a request for such comment.

(c) *When submitted.* Information amendments to the IND should be submitted as necessary but, to the extent feasible, not more often than every 30 days.

§ 312.12 IND safety reports.

(a) *Review of safety information.* The sponsor shall immediately review all information relevant to the safety or the drug obtained or otherwise received by the sponsor from any source, foreign or domestic, including information derived from clinical investigations, animal investigations, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers. For purposes of this paragraph, "information relevant to the safety of the drug" includes information about related drugs.

(b) *IND safety reports.* (1) The sponsor shall notify FDA and all participating investigators in an IND safety report of the following:

(i) Any serious adverse experiences or other information associated with the use of the drug not previously reported (in nature, severity, or incidence) that may suggest significant hazards, contraindications, side effects, or precautions. Such notification shall be made as soon as possible and in no event later than 10 working days after the sponsor's initial receipt of the information;

(ii) Any fatal or life-threatening clinical experiences associated with the use of the drug not previously reported (in nature, severity, or incidence). Such notification shall be made as soon possible and in no event later than 3 working days after the sponsor's initial receipt of the report.

(iii) For purposes of this paragraph, "associated with the use of the drug" means there is a reasonable possibility that the event may have been caused by the drug.

(2) The sponsor shall transmit each IND safety report by telephone within the time frames specified in paragraph (b)(1) of this section and shall concurrently submit a written notification. Each written notification shall bear prominent indentification of its contents, i.e., "10-Day IND Safety Report" or "3-Day IND Safety Report." Each written notification and telephone call to FDA shall be transmitted to the FDA division with responsibility for review of the IND.

(c) *Followup.* The sponsor shall promptly investigate all safety information received by it. Followup information to 3-day and 10-day reports shall be submitted promptly in an information amendment, as soon as the relevant information is available. Results of sponsor's investigation of other safety information shall be submitted, as appropriate, in an information amendment or annual report.

§ 312.33 Annual reports.

A sponsor shall submit, at intervals of 1 year after the date of submission of the IND, a brief report on the progress of the investigation containing the following:

(a) A brief summary of the status of each of the clinical studies in progress,

including the name of the investigator and the approximate number of patients under study.

(b) A brief summary of information obtained during the previous year's clinical and nonclinical investigations that is relevant to assessing the drug's safety, including: (1) A summary of all IND safety reports submitted during the past year in accordance with § 312.32; (2) a list of subjects who died during participation in an investigation, with the cause of death for each subject; and (3) a list of subjects who dropped out of an ongoing investigation.

(c) A description of the general investigational plan for the coming year to replace that submitted 1 year earlier. The general investigational plan shall contain the information required under § 312.23(a)(4).

(d) If the investigator brochure has been revised, a description of the revision and a copy of the new brochure.

(e) A description of any significant Phase 1 protocol modifications made during the previous year and not previously reported to the IND in a protocol amendment.

(f) A brief summary of significant foreign marketing developments with the drug during the past year, such as approval for marketing in any country or withdrawal from marketing in any country.

(g) If desired by the sponsor, a log of any outstanding business with respect to the IND for which the sponsor requests or expects a reply, comment, or meeting.

§ 312.34 Treatment use of an investigational new drug.

(a) *General.* A drug that is not approved for marketing may be under clinical investigation for a serious disease condition in patients for whom no satisfactory alternative drug or other therapy is available. During the clinical investigation of the drug, it may be appropriate to use the drug in the treatment of patients after sufficient evidence of the drug's safety and effectiveness has been obtained to warrant such use. Ordinarily, a drug may be made available for treatment under this section only after Phase 2 investigations have been completed, but FDA may permit such use earlier in the investigational process if compelling circumstances warrant. Administration of an investigational drug under this section serves both to provide treatment and the investigational purpose of gathering additional data on the drug's safety and effectiveness.

(b) *Treatment protocol submitted by IND sponsor.* A sponsor of a clinical investigation of a drug who intends to sponsor a treatment use for the drug under this section shall submit to FDA a treatment protocol. A treatment use under a treatment protocol may begin 30 days after FDA receives the protocol or on earlier notification by FDA that the treatment use described in the protocol may begin.

(1) A treatment protocol is required to contain the following:

(i) The intended use of the drug.

(ii) An explanation of the rationale for use of the drug, including, as appropriate, either a list of what available regimens ordinarily should be tried before using the investigational drug or an explanation of why the use of the investigational drug is preferable to the use of available marketed treatments.

(iii) A brief description of the criteria for patient selection.

(iv) The method of administration of the drug and the dosages to be used.

(v) A description of clinical procedures, laboratory tests, or other measures to be taken to monitor the effects of the drug and to minimize risk.

(2) A treatment protocol is required to be supported by the following information:

(i) A copy of the informational brochure that is to be supplied to each treating physician.

(ii) The technical information that is relevant to determining the safety and effectiveness of the drug for the intended treatment purpose. Information that is already contained in the sponsor's IND may be incorporated by reference.

(iii) If a waiver from IRB review an approval requirements is desired, a request for the waiver. (FDA may on its own initiative waive IRB review under Part 56 if it finds such review unnecessary for the protection of subjects to be treated.)

(c)(1) *Treatment IND submitted by licensed practitioner.* If a sponsor of a clinical investigation of a drug has not established a treatment protocol for the drug under paragraph (b) of this section, but the drug is being investigated by the sponsor under an effective IND, a licensed medical practitioner may seek to obtain the drug from such sponsor and submit a treatment IND to FDA requesting authorization to use the investigational drug for treatment use. A treatment use under a treatment IND may begin 30 days after FDA receives the IND or on earlier notification by FDA that the treatment use under the IND may begin. A treatment IND is required to contain the following:

(i) A cover sheet (Form FDA–1571) meeting the requirements of § 312.23(a)(1).

(ii) Information on the drug's chemistry, manufacturing, and control, and prior clinical and nonclinical experience with the drug submitted in accordance with the requirements of § 312.23. The provision of an investigational drug to a licensed medical practitioner by a sponsor of a separate clinical investigation that is subject to an IND shall be deemed to authorize the incorporation by reference of the technical information contained in the sponsor's IND into the medical practitioner's treatment IND.

(iii) A treatment protocol containing the following:

(*a*) The intended use of the drug.

(*b*) An explanation of the rationale for use of the drug, including, as appropriate, an explanation of the regimens that have perviously been tried or why use of the investigational drug is preferable to the use of available marketed treatments.

(*c*) A brief description of the criteria for patient selection.

(*d*) The method of administration of the drug and the dosages to be used.

(*e*) A description of clinical procedures, laboratory tests, or other measures to be taken to monitor the effects of the drug and minimize risks.

(iv) If a waiver from IRB review and approval requirements is desired, a request for the waiver. (FDA may on its own initiative waive IRB review requirements under Part 56, if it finds such review unnecessary for protection of subjects to be treated.)

(v) A statement of the practitioner's qualifications to use the investigational drug for the intended treatment use.

(vi) A statement that the practitioner has read or is otherwise familiar with information on the drug's safety and effectiveness derived from previous clinical and nonclinical experience with the drug.

(vii) A commitment to report to FDA adverse drug effects in accordance with § 312.56(c).

(2) A licensed practitioner who submits a treatment IND under this section is the sponsor-investigator for such IND and is responsible for meeting all applicable sponsor and investigator responsibilities under this part and Parts 50, 52, 54, and 56.

(d) *Criteria.* FDA may permit an investigational drug to be used for a treatment use under a treatment protocol or treatment IND unless it finds one of the following:

(1) The application does not fall within the terms of this section as it does not involve the treatment use of an investigational new drug intended for a serious disease condition in patients for

whom no satisfactory alternative drug or other therapy is available.

(2) The potential risks outweigh the potential benefits of the drug in the treatment of patients.

(3) There is not sufficient evidence of the drug's safety and effectiveness to justify its intended treatment use.

(e) *Agency assistance.* FDA will provide assistance to persons interested in submitting an application under this section.

§ 312.36 Emergency use of an investigational new drug.

Need for an investigational drug may arise in an emergency situation that does not allow time for submission of an IND in accordance with § 312.23. In such a case, FDA may authorize shipment of the drug for a specified use in advance of submission of an IND. A request for such authorization may be transmitted to FDA by telephone or other rapid communication means. Except in extraordinary circumstances, such authorization will be conditioned on the sponsor making an appropriate IND submission as soon as practicable after receiving the authorization.

§ 312.38 Withdrawal of an IND.

(a) At any time a sponsor may withdraw an effective IND without prejudice.

(b) If an IND is withdrawn, FDA shall be so notified, all clinical investigations conducted under the IND shall be ended, all current investigators notified, and all stocks of the drug returned or otherwise disposed of in accordance with the requirements of Part 52.

(c) If an IND is withdrawn because of a safety reason, the sponsor shall promptly so inform FDA, all participating investigators, and all reviewing Institutional Review Boards, together with the reasons for such withdrawal.

Subpart C—Administrative Actions

§ 312.40 General requirements for use of an investigational new drug in a clinical investigation.

(a) An investigational new drug may be used in a clinical investigation if the following conditions are met:

(1) The sponsor of the investigation submits an IND for the drug to FDA; the IND is in effect under paragraph (b) of this section; and the sponsor complies with all applicable requirements in this part and Parts 50, 52, 54, and 56 with respect to the conduct of the clinical investigations, and

(2) Each participating investigator conducts his or her investigation in compliance with the requirements of this part and Parts 50, 54, and 56.

(b) An IND goes into effect

(1) 30 days after FDA receives the IND, unless FDA notifies the sponsor that the investigations described in the IND are subject to a clinical hold under § 312.42, or

(2) on earlier notification by FDA that the clinical investigations in the IND may begin. FDA will notify the sponsor in writing of the date it receives the IND.

(c) A sponsor may ship an investigational new drug to investigators named in the IND:

(1) 30 days after FDA receives the IND; or

(2) on earlier FDA authorization to ship the drug.

Investigators may not, however, administer the investigational new drug to human subjects until the IND goes into effect under paragraph (b) of this section.

§ 312.41 Comment and advice on an IND.

(a) FDA may at any time during the course of the investigation communicate with the sponsor orally or in writing about deficiencies in the IND or about FDA's need for more data or information.

(b) On the sponsor's request, FDA will provide advice on specific matters relating to an IND. Such advice may include, for example, advice on the adequacy of technical data to support an investigational plan, on the design of a clinical trial, or on whether proposed investigations are likely to produce the data and information that is needed to meet requirements for a marketing application.

(c) FDA communications with a sponsor under this section are solely advisory and do not require any modification in the planned or ongoing clinical investigations or response to the agency, unless the communication is accompanied by a clinical hold order under § 312.42.

§ 312.42 Clinical holds and requests for modification.

(a) *General.* A clinical hold is an order issued by FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. The clinical hold order may apply to one or more of the investigations covered by an IND. When a proposed study is placed on clinical hold, subjects may not be given the investigational drug by the clinical investigator conducting the study. When an ongoing study is placed on clinical hold, no new subjects may be recruited to the study and placed on the investigational drug; patients already in the study should be taken off therapy under the protocol unless specifically permitted by FDA in the interest of patient safety.

(b) *Grounds for imposition of clinical hold.*—(1) *Clinical hold of a Phase 1 study under an IND.* FDA may place a proposed or ongoing Phase 1 investigation on clinical hold if it finds that:

(i) Human subjects are or would be exposed to an unreasonable and significant risk of illness or injury;

(ii) The clinical investigators named in the IND are not qualified by reason of their scientific training and experience to conduct the investigation described in the IND;

(iii) The investigator brochure is misleading, erroneous, or materially incomplete; or

(iv) The IND does not contain sufficient information required under § 312.23 to assess the risks to subjects of the proposed studies.

(2) *Clinical hold of a Phase 2 or 3 study under an IND.* FDA may place a proposed or onging Phase 2 or 3 investigation on clinical hold if it finds that:

(i) Any of the conditions in paragraph (b)(1)(i) through (iv) of this section apply, or;

(ii) The plan or protocol for the investigation is clearly deficient in design to meet its stated objectives.

(c) *Discussion of deficiency.* Whenever FDA concludes that a deficiency exists in a clinical investigation that may be grounds for the imposition of a clinical hold, FDA will, before issuing the clinical hold order, attempt to discuss and satisfactorily resolve the matter with the sponsor.

(d) *Imposition of clinical hold.* The initial clinical hold order may be made by telephone or other means of rapid communication or in writing. The clinical hold order shall be made by or on behalf of the Division Director with responsibility for review of the IND. Within 15 days of the imposition of the clinical hold, the Division Director will provide the sponsor a written explanation of the basis for the hold.

(e) *Resumption of clinical investigations.* If, by the terms of the clinical hold order, resumption of the affected investigation is permitted without prior notification by FDA once a stated correction or modification is made, the investigation may proceed as soon as the correction or modification is made. In all other cases, an investigation may only resume after the Division Director with responsibility for review of the IND has notified the sponsor that the investigation may proceed. In these cases the Division

Director will authorize resumption of the affected investigation(s) when the sponsor corrects the deficiency(ies) previously cited by the Division Director or otherwise satisfies the Division Director that the investigation(s) can proceed.

(f) *Appeal.* If the sponsor disagrees with the reasons cited for the clinical hold, the sponsor may request reconsideration of the decision in accordance with § 312.48.

(g) *Conversion of IND on clinical hold to inactive status.* If all investigations covered by an IND remain on clinical hold for 1 year or more, the IND may be placed on inactive status by FDA under § 312.45.

§ 312.44 Termination.

(a) *General.* This section describes the procedures under which FDA may terminate an IND. If an IND is terminated, the sponsor shall end all clinical investigations conducted under the IND and recall or otherwise provide for the disposition of all unused supplies of the drug. A termination action may be based on deficiencies in the IND or in the conduct of an investigation under an IND. Except as provided in paragraph (d) of this section, a termination shall be preceded by a proposal to terminate by FDA and an opportunity for the sponsor to respond. FDA will, in general, only initiate an action under this section after first attempting to resolve differences informally or, when appropriate, through the clinical hold procedures described in § 312.42.

(b) *Grounds for termination.*—(1) *Phase 1.* FDA may propose to terminate a Phase 1 IND if it finds that:

(i) Human subjects would be exposed to an unreasonable and significant risk of illness or injury.

(ii) The IND does not contain sufficient information required under § 312.23 to assess the safety to subjects of the clinical investigations.

(iii) The methods, facilities, and controls used for the manufacturing, processing, and packing of the investigational drug are inadequate to establish and maintain appropriate standards of identity, strength, quality and purity as needed for subject safety.

(iv) The clinical investigations are not being conducted in accordance with the plan or protocols submitted in the IND.

(v) The drug is being promoted or distributed for commercial purposes not justified by the requirements of the investigation or permitted by § 312.7.

(vi) The IND, or any amendment or report to the IND, contains an untrue statement of a material fact or omits material information required by this part.

(vii) The sponsor fails promptly to investigate and inform the Food and Drug Administration and all investigators of newly found serious or potentially serious hazards, contraindications, side effects, and precautions pertinent to the safety of the new drug or fails to make any other report required under this part.

(viii) The sponsor fails to submit an accurate annual report of the investigations in acordance with § 312.33.

(ix) The sponsor fails to comply with any other applicable requirement of this part or Part 50, 52, 54, or 56.

(x) The IND has remained on inactive status for 5 years or more.

(2) *Phase 2 or 3.* FDA may propose to terminate an IND during Phase 2 or Phase 3 if FDA finds that:

(i) Any of the conditions in paragraph (b)(1)(i) thorugh (x) of this section apply; or

(ii) The investigational plan or protocol(s) is not reasonable as a bona fide scientific plan to determine whether or not the drug is safe and effective for use; or

(iii) There is convincing evidence that the drug is effective for the purpose for which it is being investigated.

(c) *Opportunity for sponsor response.* (1) If FDA proposes to terminate an IND, FDA will notify the sponsor in writing, and invite correction or explanation within a period of 30 days.

(2) On such notification, the sponsor may provide a written explanation or correction or may request a conference with FDA to provide the requested explanation or correction. If the sponsor does not respond to the notification within the allocated time, the IND shall be terminated.

(3) If the sponsor responds but FDA does not accept the explanation or correction submitted, FDA shall inform the sponsor in writing of the reason for the nonacceptance and provide the sponsor with an opportunity for a regulatory hearing before FDA Under Part 16 on the question of whether the IND should be terminated. The sponsor's request for a regulatory hearing must be made within 10 days of the sponsor's receipt of FDA's notification of nonacceptance.

(d) *Immediate termination of IND.* Notwithstanding paragraphs (a) through (c) of this section, if at any time FDA concludes that continuation of the investigation presents a significant danger to the public health, the agency shall immediately, by written notice to the sponsor from the Director of the National Center for Drugs and Biologics, terminate the IND. An IND so terminated is subject to reinstatement by the Director on the basis of additional submissions that eliminate such danger. If an IND is terminated under this paragraph, the agency will afford the sponsor an opportunity for a regulatory hearing under Part 16 on the question of whether the IND should be reinstated.

§ 312.45 Inactive status.

(a) If no subjects are entered into clinical studies for a period of 2 years or more under an IND, or if all investigations under an IND remain on clinical hold for 1 year or more, the IND may be placed by FDA on inactive status. This action may be taken by FDA either on request of the sponsor or on FDA's own initiative. If FDA seeks to act on its own initiative under this section, it shall first notify the sponsor in writing of the proposed inactive status. Upon receipt of such notification, the sponsor shall have 30 days to respond as to why the IND should continue to remain active.

(b) If an IND is placed on inactive status, all investigators shall be so notified and all stocks of the drug shall be returned or otherwise disposed of as described in Part 52.

(c) A sponsor is not required to submit annual reports to an IND on inactive status. An inactive IND is, however, still in effect for purposes of the public disclosure of data and information under § 312.130.

(d) A sponsor who intends to resume clinical investigation under an IND placed on inactive status shall submit a protocol amendment under § 312.30 containing the proposed general investigational plan for the coming year and appropriate protocols. If the protocol amendment relies on information previously submitted, the plan shall reference such information. Additional information supporting the proposed investigation, if any, shall be submitted in an information amendment Notwithstanding the provisions of § 312.30, clinical investigations under an IND on inactive status may only resume (1) 30 days after FDA receives the protocol amendment, unless FDA notifies the sponsor that the investigations described in the amendment are subject to a clinical hold under § 312.42, or (2) on earlier notification by FDA that the clinical investigations described in the protocol amendment may begin.

(e) An IND that remains on inactive status for 5 years or more may be terminated under § 312.44.

§ 312.47 Meetings.

(a) *General.* Meetings between a sponsor and the agency are frequently useful in resolving questions and issues raised during the course of a clinical investigation. FDA encourages such meetings to the extent that they aid evaluation of the drug and the solution of scientific problems concerning the drug and to the extent that FDA's resources permit. The general principle underlying the conduct of such meetings is that there should be free, full, and open communication about any scientific or medical question that may arise during the clinical investigation. These meetings shall be conducted and documented in accordance with Part 10.

(b) *"End-of-Phase 2" meetings and meetings held before submission of a marketing application.* At specific times during the drug investigation process, meetings between FDA and a sponsor can be especially helpful in minimizing wasteful expenditures of time and money and thus in speeding the drug development and evaluation process. In particular, FDA has found that meetings at the end of Phase 2 of an investigation (end-of-Phase 2 meetings) are of considerable assistance in planning later studies and that meetings held near completion of Phase 3 and before submission of a marketing application ("pre-NDA" meetings) are helpful in developing methods of presentation and submission of data in the marketing application that facilitate review and allow timely FDA response.

(1) *End-of-Phase 2 meetings.*—(i) *Purpose.* The purpose of an end-of-Phase 2 meeting is to determine the safety of proceeding to Phase 3, to evaluate the Phase 3 plan and protocols, and to identify any additional information necessary to support a marketing application for the uses under investigation.

(ii) *Eligibility for meeting.* The end-of-Phase 2 meeting is designed primarily for IND's involving new molecular entities or major new uses of marketed drugs. However, a sponsor of any IND may request and obtain an end-of-Phase 2 meeting.

(iii) *Timing.* To be most useful to the sponsor, end-of-Phase 2 meetings should be held before major commitments of effort and resources to specific Phase 3 tests are made. The scheduling of an end-of-Phase 2 meeting is not, however, intended to delay the transition of an investigation from Phase 2 to Phase 3.

(iv) *Advance information.* At least 1 month in advance of an end-of-Phase 2 meeting, the sponsor should submit background information on the sponsor's plan for Phase 3, including summaries of the Phase 1 and 2 investigations, the specific protocols for Phase 3 clinical studies, plans for any additional nonclinical studies, and, if available, tentative labeling for the drug. The recommended contents of such a submission are described more fully in an FDA Staff Manual Guide (NCDB 4850.6) that is publicly available under FDA's public information regulations in Part 20.

(v) *Conduct of meeting.* Arrangements for an end-of-Phase 2 meeting are to be made with the division responsible for review on the IND. The meeting will be scheduled by FDA at a time convenient to both FDA and the sponsor. Both the sponsor and FDA may bring consultants to the meeting. The meeting should be directed primarily at establishing agreement between FDA and the sponsor of the overall plan for Phase 3 and the objectives and design of particular studies. The adequacy of technical information to support Phase 3 studies and/or a marketing application may also be discussed. Agreements reached at the meeting on these matters will be recorded in minutes of the conference that will be taken by FDA in accordance with § 10.65 and provided to the sponsor. The minutes along with any other written material provided to the sponsor will serve as a permanent record of any agreements reached. Barring a significant scientific development that requires otherwise, studies conducted in accordance with the agreement shall be presumed to be sufficient in objective and design for the purpose of obtaining marketing approval for the drug.

(2) *"Pre-NDA" meetings.* FDA has found that delays associated with the initial review of a marketing application may be reduced by exchanges of information about a proposed marketing application. The primary purpose of this kind of exchange is to acquaint FDA reviewers with the general information to be submitted in the marketing application, to uncover any major unresolved problems, to identify those studies that the sponsor is relying on as adequate and well-controlled to establish the drug's effectiveness, to discuss appropriate methods for statistical analysis of the data, and to discuss the best approach to the presentation and formatting of data in the marketing application. Arrangements for such a meeting are to be made by the sponsor with the division responsible for review of the IND. To permit FDA to provide the sponsor with the most useful advice on preparing a marketing application, the sponsor should submit to FDA's reviewing division at least 1 month in advance of the meeting the following information:

(i) A brief summary of the clinical studies to be submitted in the application.

(ii) A Proposed format for organizing the submission, including methods for presenting the data.

§ 312.48 Request for reconsideration or clarification of technical requirements or informal opinions.

FDA is committed to resolving differences between sponsors and FDA reviewing divisions with respect to IND's as quickly and amicably as possible through the cooperative exchange of information and views. That exchange may take place through written correspondence, telephone conversations, or informal meetings. In addition, FDA has established administratively a specific procedure under which a sponsor may ask the agency to reconsider or clarify an agency action or an informal opinion expressed to a sponsor by an agency employee with respect to an IND. Examples of issues contemplated for resolution under the procedure include requests by FDA for specific studies or information, requests to modify or delay a study, and unfavorable responses by FDA to requests from sponsors for waivers or special technical approaches to a scientific problem. The procedure will be marked by the sponsor's submission of a written request for reconsideration of clarification to the division that is responsible for reviewing the application, the division's prompt response to the applicant, and, if the division's response is not acceptable to the applicant, automatic review of the issue by managment to the National Center for Drugs and Biologics. FDA will attempt to issue a final decision within 60 days of the applicant's request. This procedure is described more fully in an FDA Staff Manual Guide (NCDB 4820.5) that is publicly available under FDA's public information regulations in Part 20.

Subpart D—Responsibilities of Sponsors and Investigators

§ 312.50 General responsibilities of sponsors.

Sponsors are responsible for selecting qualified investigators, providing them with the information they need to conduct an investigation properly, ensuring proper monitoring of the investigation(s), ensuring that the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in the IND, maintaining an effective IND with respect to the

investigations, and ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug. Additional specific responsibilities of sponsors are described elsewhere in this part and in Part 52.

§ 312.53 Selecting investigators and monitors.

(a) *Selecting investigators.* A sponsor shall select only investigators qualified by training and experience as appropriate experts to investigate the drug.

(b) *Control of drug.* A sponsor shall ship investigational new drugs only to investigators participating in the investigation.

(c) *Obtaining information from the investigator.* The sponsor shall obtain from each clinical investigator the following:

(1) A signed investigator statement (Form FDA–1572) containing:

(i) The name and address of the investigator;

(ii) The name and code number, if any, of the protocol(s) in the IND identifying the study(ies) to be conducted by the investigator.

(iii) The name and address of any medical school, hospital, or other research facility where the clinical investigation(s) will be condicted;

(iv) The name and address of any clinical laboratory facilities to be used in the study;

(v) The name and address of the IRB that is responsible for review and approval of the study(ies);

(vi) A commitment by the investigator that he or she—

(*a*) Will conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after consultation with the sponsor;

(*b*) Will comply with all requirements of Part 54 regarding the obligations of clinical investigators and all other pertinent requirements in this part;

(*c*) Will personally conduct or supervise the described investigation(s);

(*d*) Will ensure that the requirements relating to obtaining informed consent and institutional review board review and approval are met;

(*e*) Will report to the sponsor immediately any unsuspected or serious side effects that occur in the course of the investigation(s);

(*f*) Has read and understands the information in the investigator's brochure, including the potential risks and side effects of the drug; and

(*g*) Will ensure that all associated, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

(vii) A list of the names of the subinvestigators (e.g., research fellows, residents, colleagues) who will be assisting the investigator in the conduct of the investigation(s).

(2) *Curriculum vitae.* A curriculum vitae for the investigator showing the education, training, and experience that qualifies the investigator as an expert in the clinical investigation of the drug for the use under investigation.

(3) *Clinical plan.* (i) For Phase 1 investigations, a general outline of the planned investigation including the estimated duration of the study and the maximum number of subjects that will be involved.

(ii) For Phase 2 or 3 investigations, an outline of the plan of investigation including an approximation of the number of subjects to be treated with the drug and the number to be employed as controls, if any; the clinical uses to be investigated; characteristics of subjects by age, sex, and condition; the kind of clinical observations and laboratory tests to be conducted; the estimated duration of the study; and copies or a description of case report forms to be used.

(d) *Selecting monitors.* A sponsor shall select a monitor qualified by training and experience to monitor the investigation in accordance with this part and Part 52.

§ 312.55 Informing investigators.

(a) Before the investigation begins, a sponsor (other than a sponsor-investigator) shall give each participating clinical investigator an investigator brochure containing the information described in § 312.23(a)(5).

(b) The sponsor shall, as the overall investigational plan proceeds, keep each participating investigator informed of new observations discovered by or reported to the sponsor on the drug, particularly with respect to adverse effects and safe use. Such information may be distributed to investigators by means of periodically revised investigator brochures, reprints or published studies, reports or letters to clinical investigators, or other appropriate means. Important safety information should be relayed orally, but shall be followed as soon as practicable by a written communication.

§ 312.56 Monitoring investigations.

(a) A sponsor who discovers that an investigator is not complying with the signed agreement (Form FDA–1572), the general investigational plan, or the requirements of this part or other applicable parts shall promptly either secure compliance or discontinue shipments of the investigational new drug to the investigator and end the investigator's participation in the investigation. If the investigator's participation in the investigation is ended, the sponsor shall require that the investigator dispose of or return the investigational drug in accordance with the requirements of Part 52 and shall notify FDA.

(b) The sponsor shall monitor the progress of all clinical and nonclinical investigations and evaluate the evidence relating to the safety and effectiveness of the drug as it is obtained from the investigators. The sponsors shall make such reports to FDA regarding adverse drug experiences as are required under § 312.31.

(c) A sponsor who determines that safety information presents an unreasonable and significant risk to subjects shall discontinue those investigations that present the risk, notify FDA, all institutional review boards, and all investigators who have at any time participated in the investigation of the discontinuance, assure the disposition of all stocks of the drug outstanding as required by § 52.41, and furnish FDA with a full report of the sponsor's actions. The sponsor shall discontinue the investigation as soon as possible, and in no event later tha 5 working days after making the determination that the investigation should be discontinued. Upon request, FDA will confer with a sponsor on the need to discontinue an investigation.

§ 312.58 Inspection of sponsor's records and reports.

(a) Upon the request at reasonable times of a scientifically trained and properly authorized employee of FDA, the sponsor shall make available for inspection and copying the records and reports required to be maintained under this part and under other applicable parts of this chapter. Upon written request by FDA, the sponsor shall submit the records or reports (or copies of them) to FDA. The sponsor shall discontinue shipments of the drug to any investigator who has failed to maintain or make available records or reports of the investigation as required by this part or Part 54.

(b) If an investigational new drug is a substance listed in any schedule of the Controlled Substances Act (21 U.S.C. 801; 21 CFR 1308), records concerning shipment, delivery, receipt, and disposition of the drug, which are required to be kept under this part or other applicable parts of this chapter

shall, upon the request of a properly authorized employee of the Drug Enforcement Administration of the U.S. Department of Justice, be made available by the investigator or sponsor to whom the request is made, for inspection and copying.

§ 312.60 General responsibilities of investigators.

An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan and applicable regulations, for protecting the rights, safety, and welfare of subjects under the investigator's care and for the control of drugs under investigation. Specific responsibilities of clinical investigators are set forth in Parts 54 and 56.

§ 312.62 Investigator records and reports.

An investigator shall make such reports and maintain such records as are required in accordance with Part 54.

Subpart E—Miscellaneous

§ 312.63 Import and export requirements.

(a) *Imports.* An investigational new drug offered for import into the United States complies with the requirements of this part if it is subject to an effective IND under § 312.40 and either (1) the consignee in the United States is the sponsor of the IND or (2) the consignee is a qualified investigator named in the IND.

(b) *Exports.* An investigational new drug intended for export from the United States complies with the requirements of this part as follows:

(1) If an IND is in effect for the drug under § 312.40 and each person who receives the drug is an investigator named in the application; or

(2) If FDA authorizes shipment of the drug for use in clinical investigation. Authorization may be obtained as follows:

(i) Through submission to FDA of a written request from the person that seeks to export the drug. A request must provide adequate information about the drug to satisfy FDA that the drug is appropriate for the proposed investigational use in humans, that the drug will be used for investigational purposes only, and that the drug may be legally used by that consignee in the importing country for the proposed investigational use. The request shall specify the quantity of the drug to be shipped per shipment and the frequency of expected shipments. If FDA authorizes exportation under this subparagraph, the agency shall concurrently notify the government of the importing country of such authorization.

(ii) Through submission to FDA of a formal request from an authorized official of the government of the country to which the drug is proposed to be shipped. A request must specify that the foreign government has adequate information about the drug and the proposed investigational use, that the drug will be used for investigational purposes only, and that the foreign government is satisfied that the drug may legally be used by the intended consignee in that country.

(iii) Authorization to export an investigational drug under paragraph (b)(2) (i) or (ii) of this section may be revoked by FDA if the agency finds that the conditions underlying its authorization are no longer met.

(3) This paragraph applies only where the drug is to be used for the purpose of clinical investigation. Export of an investigational drug for commercial marketing or for use in routine medical practice is not permitted.

§ 312.120 Foreign clinical studies not conducted under an IND.

(a) *Introduction.* This section describes the criteria for acceptance by FDA of foreign clinical studies not conducted under an IND. In general, FDA accepts such studies provided they are well designed, well conducted, performed by qualified investigators, and conducted in accordance with ethical principles acceptable to the world community. Studies meeting these criteria may be utilized to support clinical investigations in the United States and/or marketing approval. Marketing approval of a new drug or antibiotic drug based solely on foreign clinical data is governed by § 314.106 (proposed in the **Federal Register** of October 19, 1982; 47 FR 46622, 46655).

(b) *Data submissions.* A sponsor who wishes to rely on a foreign clinical study to support a U.S. study in the IND shall submit to FDA the following information:

(1) A description of the investigator's qualification;

(2) A description of the research facilities;

(3) A detailed summary of the protocol and results of the study, and, should FDA request, case records maintained by the investigator or additional background data such as hospital or other institutional records;

(4) A description of the drug substance and drug product used in the study, including a description of components, formulation, specifications and bioavailability of the specific drug product used in the clinical study, if available; and

(5) If the study is intended to support the effectiveness of a drug product, information showing that the study is adequate and well controlled under § 314.126 (proposed in the **Federal Register** of October 19, 1982; 47 FR 46622, 46656).

(c) *Conformance with ethical principles.* (1) Foreign clinical research is required to have been conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" (see paragraph (c)(5) of this section) or the laws and regulations of the country in which the research was conducted, whichever represents the greater protection of the individual.

(2) For each foreign clinical study submitted under this section, the sponsor shall explain how the research conformed to the ethical principles contained in the "Declaration of Helsinki" or the foreign country's standards, whichever were used. If the foreign country's standards were used, the sponsor shall explain in detail how those standards differ from the "Declaration of Helsinki" and how they offer greater protection.

(3) When the research has been approved by an independent review committee, the sponsor shall submit to FDA documentation of such review and approval, including the names and qualifications of the members of the committee. In this regard, a "review committee" means a committee composed of scientists and, where practicable, individuals who are otherwise qualified (e. g., other health professionals or laymen). The investigator may not vote on any aspect of the review of his or her protocol by a review committee.

(4) When the research has not been approved by a review committee, the sponsor shall describe how the research conformed to the ethical standards in the country in which the research was conducted, so as to meet the goals of the "Declaration of Helsinki" In compensating for the lack of review committee approval.

(5) The "Declaration of Helsinki" states as follows:

Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects

I. *Basic Principles*

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted to a specially appointed independent committee for consideration, comment and guidance.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Doctors should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Doctors should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the doctor is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she is free to withdraw his or her consent to participation at any time. The doctor should then obtain the subject's given informed consent, preferable in writing.

10. When obtaining informed consent for the reasearch project the doctor should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a doctor who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. Medical Research Combined With Professional Care (Clinical Research)

1. In the treatment of the sick person, the doctor must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient—including those of a control group, if any—should be assured of the best proven diagnostic and therapeutic methods.

4. The refusal of the patient to participate in a study must never interfere with the doctor-patient relationship.

5. If the doctor considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).

6. The doctor can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. Non-Therapeutic Biomedical Research Involving Human Subjects (Non-Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the doctor to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subjects should be volunteers—either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

§ 312.130 Availability for public disclosure of data and information in an IND.

(a) The existence of an investigational new drug application will not be disclosed by FDA unless it has previously been publicly disclosed or acknowledged.

(b) The availability for public disclosure of all data and information in an investigational new drug application for a new drug or antibiotic drug file will be handled in accordance with the provisions established in § 314.430 (proposed in the **Federal Register** of October 19, 1982; 47 FR 46664) for the confidentiality of data and information in applications submitted under Part 314. The availability for public disclosure of all data and information in an investigational new drug application for a biological product will be governed by the provisions of §§ 601.50 and 601.51.

(c) Notwithstanding the provisions of § 314.430, FDA shall disclose upon request to an individual to whom an investigational new drug has been given a copy of any IND safety report relating to the use in that individual.

§ 312.140 Address for correspondence.

(a) Except as provided in paragraph (b) of this section, a sponsor shall send an initial IND to the Documents and Records Section (HFN–106), Office of New Drug Evaluation, National Center for Drugs and Biologics, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. On receiving the IND, FDA will inform the sponsor which one of the divisions in the Office of New Drug Evaluation is responsible for the IND. Amendments, reports, and other correspondence relating to matters covered by the IND should be directed to the appropriate division. The outside wrapper of each submission shall state what is contained in the submission, for example, "IND Application", "Protocol Amendment", etc.

(b) Applications for the products listed below should be submitted to the Office of Biologics (HFN–823), National Center for Drugs and Biologics, Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20205: (1) Products subject to the licensing provisions of the Public Health Service Act of July 1, 1944 (58 Stat. 682, as amended (42 U.S.C. 201 et. seq.)) or subject to Part 600; (2) ingredients packaged together with containers intended for the collection, processing, or storage of blood or blood components; (3) urokinase products; (4) plasma volume expanders and hydroxyethyl starch for leukapheresis; and (5) coupled antibodies, i.e., products that consist of an antibody component coupled with a drug or radionuclide component in which both components provide a pharmacological effect but the biological component determines the site of action.

(c) All correspondence relating to biological products for human use which are also radioactive drugs shall be submitted to the Division of Oncology and Radiopharmaceutical Drug Products (HFN–150), Office of New Drug Evaluation, National Center for Drugs and Biologics, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, except that applications for coupled antibodies shall be submitted in accordance with paragraph (b) of this section.

(d) All correspondence relating to export of an investigational drug under § 312.110(b)(2) shall be submitted to the International Affairs Staff (HFY–50), Office of Health Affairs, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

§ 312.145 Guidelines

(a) FDA has made available guidelines under § 10.90(b) to help persons to comply with certain requirements of this part.

(b) The National Center for Drugs and Biologics maintains a list of guidelines that apply to the Center's regulations. The list states how a person can obtain a copy of each guideline. A request for a copy of the list should be directed to the Assistant Director for Regulatory Affairs (HFN–7), National Center for Drugs and Biologics, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

Subpart F—Drugs for Investigational Use in Laboratory Research Animals or In Vitro Tests

§ 312.160 Drugs for investigational use in laboratory research animals or in vitro tests.

(a) *Authorization to ship.* (1) A person may ship a drug intended solely for tests in vitro or in animals used only for laboratory research purposes if it is labeled as follows:

Caution: Contains a new drug for investigational use only in laboratory research animals, or for tests in vitro. Not for use in humans.

(2) A person shipping a drug under paragraph (a) of this section shall use due diligence to assure that the consignee is regularly engaged in conducting such tests and that the shipment of the new drug will actually be used for tests in vitro or in animals used only for laboratory research.

(3) A person who ships a drug under paragraph (a) of this section shall maintain adequate records showing the name and post office address of the expert to whom the drug is shipped and the date, quantity, and batch or code mark of each shipment and delivery. Such records are to be maintained for a period of 2 years after the shipment. Upon the request of a properly authorized FDA employee at reasonable times, the person shall make such records available for inspection and copying.

(b) *Termination of authorization to ship.* FDA may terminate authorization to ship a drug under this section, if it finds that:

(1) The sponsor of the investigation has failed to comply with any of the conditions for shipment established under this section; or

(2) The continuance of the investigation is unsafe or otherwise contrary to the public interest or the drug is used for purposes other than bona fide scientific investigation. FDS will notify the person shipping the drug of its finding and invite immediate correction. If correction is not immediately made, the person shall have an opportunity for a regulatory hearing before FDA pursuant to Part 16. If authorization to ship the drug is terminated, the person shipping the drug shall recall or have destroyed the unused supplies of the drug.

Interested persons, may, on or before August 8, 1983, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Arthur Hull Hayes, Jr.,

Commissioner of Food and Drugs.

Richard S. Schweiker,

Secretary of Health and Human Services.

Dated: February 3, 1983.

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